QUATERNARY THIAZOLIUM COMPOUNDS RELATED TO ANEURINE

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The major part of this thesis is based on four papers to which the author has contributed, viz.:-

1. Uber Aneurin, II. Mitteil.: Uber die Synthese von N-Aryl-thiazoliumsalzen; über Einzelheiten in der Konstitution des Aneurins und Thiochromes. A.R. Todd, F. Bergel und Karimullah. (Ber. 1936, 69, 217)

2. 5-Thioformamidopyrimidines. A.R.Todd, F. Bergel and Karimullah. (J. 1936, 1557)

3. Thioformylation of Amines. A.R.Todd, F. Bergel, Karimullah and R. Keller. (J. 1937, in press)

4. Some substituted phenyl and benzyl thiazolium salts. Karimullah. (Submitted to the British Chemical Society in March 1937).

Two reprints of papers 1 and 2 are attached.

Contents

Page

THEORETICAL:

Introduction 1

Synthesis of Quaternary Thiazolium Salts..... 2

Modification of Hantzsch Synthesis..... 3

A New Method of Thioformylation..... 6

Phenyl Analogue of Aneurine..... 7

Dithioformic Acid and Secondary Amines..... 13

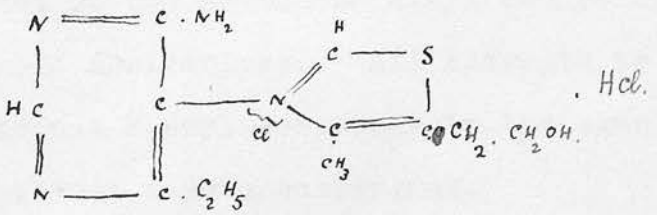
Action of Formaldehyde on pyrimidines..... 14

EXPERIMENTAL 19

THEORETICAL

Introduction

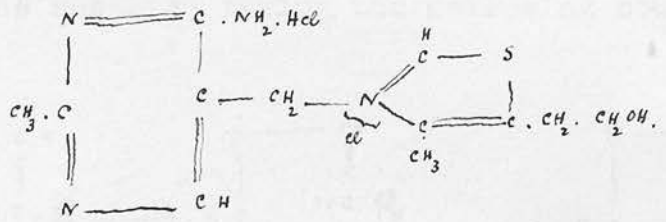
By cleavage of aneurine (vitamin B_1) with an acid solution of sodium sulphite, Williams, Waterman, Keresztesy and Buchman (J. Amer. Chem. Soc., 1935, 57, 536) obtained an acidic substance $C_6H_9O_3N_3S$, considered to be a pyrimidine sulphonic acid, and a base C_6H_9ONS, which Clarke and Gurin (ibid. p.1876) showed to be identical with 4-methyl-5-β-hydroxyethylthiazole. Largely on the basis of this work, Williams (ibid. p. 229) formulated the vitamin hydrochloride as 3-(6'-amino-4'-ethyl-pyrimidyl-5')-4-methyl-5-β-hydroxyethylthiazolium chloride hydrochloride.



The/

The aim of this work has been the synthesis of quaternary thiazolium compounds which might be of help in elucidating the constitution of aneurin.

It may be stated here that the above formula has now been slightly changed, the following modification being subsequently supported by synthesis (Williams and Cline, J. Amer. Chem. Soc., 1936, 58, 1504; Todd and Bergel, J.C.S. in press).



Synthesis of quaternary thiazolium salts.

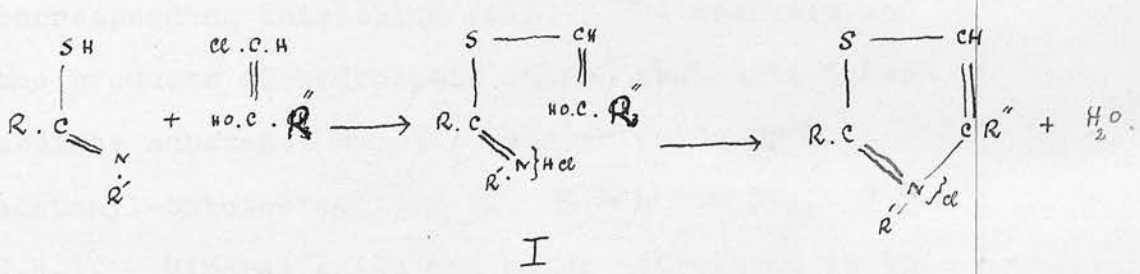
1. Addition of alkyl and benzyl halides to thiazoles.

N-alkyl and N-benzyl thiazolium compounds can easily be prepared by the action of alkyl and benzyl halides on thiazole derivatives. All attempts to prepare the analogous N-aryl compounds in the same way, from aryl halides were unsuccessful. Pyrimidines having halogen substituted in position 5 gave the same negative result.

Modification/

Modification of Hantzsch Synthesis.

The well known synthesis of thiazoles by Hantzsch was then modified so as to obtain the quaternary thiazolium salts. It was thought possible that if thioamides having the general formula R.CS.NH.R' were used instead of unsubstituted thioamides in the Hantzsch synthesis, the required thiazolium salts might be obtained. This proved to be true, the reaction taking the following course:



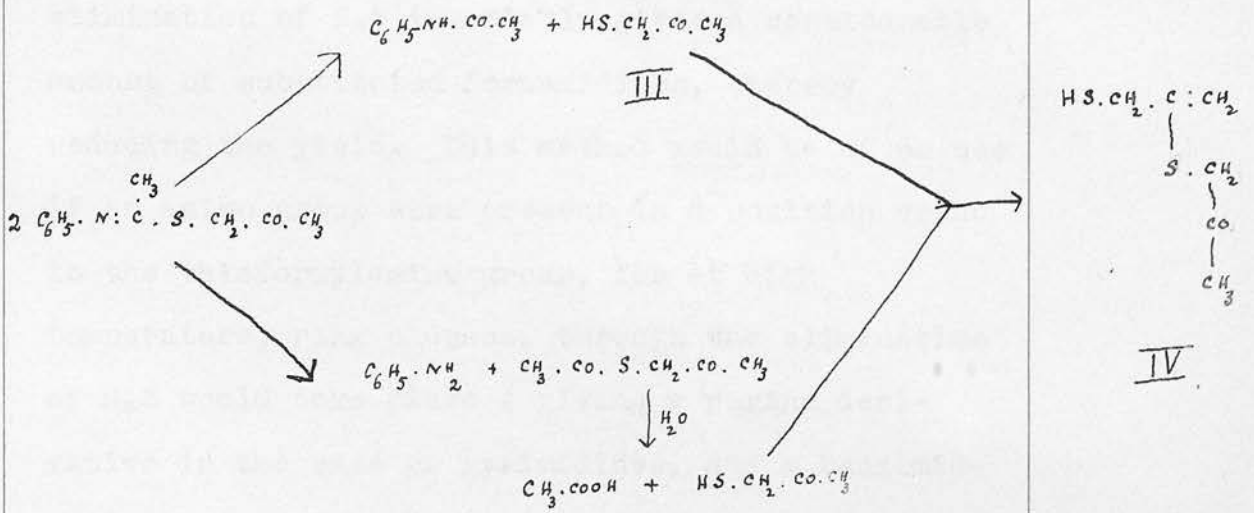
I

N-methylthioacetamide reacted readily with chloracetone in the cold giving N-methyl-2-4-dimethylthiazolium chloride in quantitative yield. (II. $R = R' = R'' = CH_3$). This compound was changed into the iodide, which gave no depression of melting point when mixed with the compound obtained/

obtained from methyl iodide and 2-4-dimethyl-thiazole. No intermediate product of the type I could be isolated in this experiment.

Thio-acetanilide when heated with chloracetone, with or without alcohol as solvent, gave directly N-phenyl-2-4-dimethylthiazolium chloride (II. R = R'' = CH_3, R' = C_6H_5). If, however, the reaction was carried out at room temperature, an unstable crystalline substance resulted, which could be changed by heating for a short time into the corresponding thiazolium salt. The analysis and the products of hydrolysis showed that this intermediate substance was the hydrochloride of S-acetonyl-thioacetanilide (I. R = R'' = CH_3, R ' = C_6H_5). Mineral acids and water hydrolysed it to aniline, acetanilide and a sulphur-containing compound which must have resulted from the condensation of two molecules of the hypothetical thiol-acetone III. On account of the analysis and the reactions of this compound (formation of semi-carbazone, formation of a colourless precipitate with $HgCl_2$ and reactions of SH group), the formula IV was assigned to it. The presence of acetanilide among the products of hydrolysis showed that the cleavage/

cleavage had taken place not only between N and C, but also between C and S according to the following scheme:



Thio-acet-o-toluidide and o-nitro-thio-acetanilide gave with chloracetone, N-o- tolyl and N-o-nitrophenyl-2-4-dimethylthiazolium chlorides respectively. In both these cases the corresponding intermediate products were isolated.

The quaternary thiazolium chlorides could be isolated in all cases, but on account of their hygroscopic nature, it was found preferable to use the iodides and in particular the perchlorates for the purposes of isolation.

In aneurin, position 2 in the thiazole nucleus is not occupied by any substituent. In order to synthesise a compound of this type, a thioformyl-amino compound must be used as starting material.

Treatment/

Treatment of formylamino compounds with P_2S_5 with or without solvent at a high temperature leads to replacement of oxygen by sulphur, although further elimination of H_2S invariably gives a considerable amount of substituted formamidines, thereby reducing the yield. This method would be of no use if an amino group were present in a position ortho to the thioformylamino group, for at high temperature, ring closure, through the elimination of H_2S would take place (giving a purine derivative in the case of pyrimidines, and a benzimidazole in the case of benzene compounds). Another method of preparing thioformylamino compounds, due to Hoffman (Ber., 1878, 11, 339) consists in the addition of H_2S to an isonitrile. This method, however, was without success in the pyrimidine series, where it was found difficult to replace the 5-amino group by an isonitrile group.

A New Method of Thioformylation

Thioacetic acid reacts readily with primary amines to give the corresponding acetyl derivatives

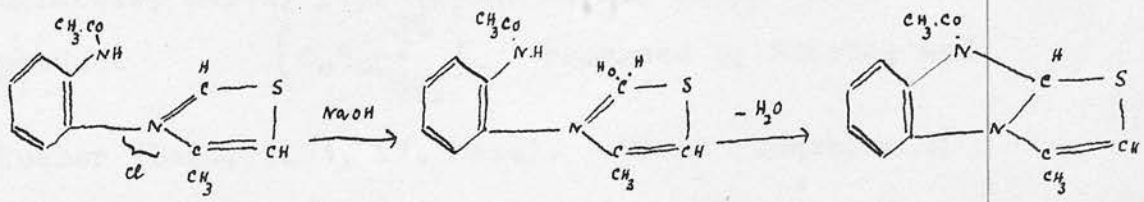
(Pawlewski/

(Pawlewski, Ber., 1898, 31, 66; 1902, 35, 110). Accordingly direct thioacylation by heating amines with dithio-acids was tried. With dithioacetic acid, this was completely successful. Dithioformic acid acts in a similar way, but the yield is not very good and the product is difficult to purify. It was, however, found that thioformylation can be easily effected by mixing aqueous solutions of the primary amino compounds and potassium dithioformate, at room temperature in an atmosphere of carbondioxide the thioformyl derivatives normally separate in almost pure condition, the yield being nearly quantitative. In the case of pyrimidines, an amino group in position 5 could be easily thioformylated; amino groups in position 2, 4 and 6 did not react in these conditions.

Phenyl Analogue of Aneurine.

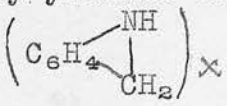
A phenyl analogue of aneurin according to the formula originally proposed by Williams (loc. cit.) would be N-o-aminophenylthiazolium chloride, for which monothioformyl o-phenylenediaminine could serve as a point of departure. The latter substance could, however, not be prepared, because the/

the thioformylation of o-phenylenediamine leads to benzimidazole. Hence mono-acetyl o-phenylene-diamine was thioformylated and then condensed with chloracetone, to form a thiazolium chloride. The acetyl group could, however, not be removed satis-factorily; on adding sodium hydroxide to the solution of the quaternary salt, a transitory turbidity appeared. After rapid extraction with ether and treatment with dry hydrochloric acid, a crystalline salt of a tertiary base was obtained, isomeric with the original substance. The new salt may be a dihydrothiazole hydrochloride and it might be formed according to the following scheme:



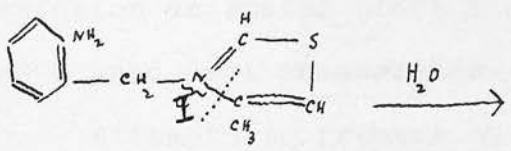
On oxidation with potassium ferricyanide in alkaline/

alkaline solution, no fluorescence was observed. After keeping for some time in dilute sodium hydroxide solution and extracting with chloroform or ether, a gum was obtained, which still contained sulphur.

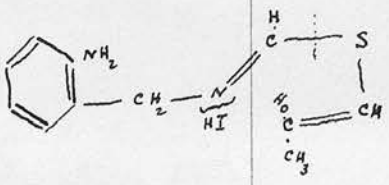
After the present formula for aneurin had been put forward and confirmed by synthesis (Williams and Cline, J. Amer. Chem. Soc., 1936, 58, 1504; Todd and Bergel, J.C.S. in the press), similar experiments were made with a view to obtaining N-o-aminobenzyl-thiazolium chloride. O-Aminobenzyl-amine on thioformylation yields dihydroquinazoline in quantitative yield. The hydrochloride of o-amino benzyl chloride, on treatment with 4-methyl-thiazole, merely yielded the highly polymerised product  recorded by Gabriel and Posner (Ber., 1894, 27, 3514). Hence reduction of N-o-nitrobenzyl-4-methyl-thiazolium chloride was resorted to. After many unsuccessful attempts, hydriodic acid and red phosphorus was found the most suitable reducing agent. The iodide so formed is rather unstable, hence it was changed into the corresponding chloride. On alkaline oxidation with potassium ferricyanide, this compound gave a blue/

blue fluorescence in ultra-violet light, but a crystalline substance like thiochrome could not be separated.

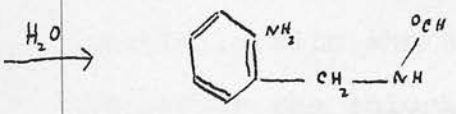
Incidentally it may be remarked that alkaline oxidation of this iodide with potassium ferricyanide invariably gave iodoform and when the same operation was repeated with other N-phenyl or benzylthiazolium iodides, a very strong smell of isonitrile was detected. This could be explained as follows:



I.



II.



III.

$HS.CH_2.CO.CH_3$

IV.

(III) closes to form a dihydroquinazoline which would be dehydrogenated to quinazoline and (IV) gives iodoform with iodine set free from NaI with/

with potassium ferricyanide during the reaction. In the case of other N-phenylthiazolium iodides having no o-amino group, the formyl group is further hydrolysed giving a primary amine, which with iodoform in alkaline medium results in the formation of isonitrile.

Thiochrome could not be obtained by oxidation of aneurin quantitatively (compare Barger, Bergel and Todd, Ber., 1935, 68, 2257), the yield being at the most 70%. It is suggested that a side reaction as stated above might lead to destruction of a good deal of aneurine.

Attempts to prepare phenyl analogue of thiochrome (according to Todd, Bergel, F. Conrat and Jacob, J. 1936, 1601) by condensing o-chlorbenzyl chloride with 2-amino-4-methylthiazole were without success. Presumably the chlormethyl group reacts preferentially with the amino group of the thiazole; moreover the chlorine in a benzene ring would be less reactive than when attached to the 6- position of a pyrimidine ring.

Finally it may be mentioned that thioformylation with potassium dithioformate has been found to be of general application and methods are described in the experimental section for carrying out the reactions with amines of widely varying types. The aliphatic thioformamido compounds are mostly liquids, but with aromatic and heterocyclic amines thioformylation/

formylation yields crystalline derivatives usually with sharp melting points which are useful for identification. In the case of o-phenylene-diamine an unstable thioformyl derivative can be obtained which passes slowly into benzimidazole. With o-aminobenzylamine potassium dithioformate even at room temperature causes immediate production of dihydroquinazoline; no thioformyl derivative could be obtained. The ease with which ring closure occurs in these cases suggests that thio-acylamido derivatives might advantageously be employed in such reactions where acylamido derivatives are commonly used.

Glycocoll ester hydrochloride, when thioformylated in the usual way gave a yellowish oily product which was not purified further. It was directly condensed with chloracetone to give the quaternary thiazolium salt, the ester group being, however, hydrolysed during condensation.

It will not be out of place to remark that 5-, 6- and 8-thioformylaminoquinolines did not give quaternary thiazolium salts with chloracetone. Under even the mildest conditions hydrogen sulphide escaped and in each case a yellow crystalline compound was obtained which contained no sulphur and which/

which was very soluble in alcohol and in water. The exact composition of these compounds could not, however, be ascertained.

Although dithioformic acid or its potassium salt reacts readily with most primary amines, there are certain exceptions to this rule. As has already been stated above, amino groups - or rather imino groups - in positions 2, 4 and 6 of the pyrimidine nucleus could not be thioformylated by this method. Similarly amino groups in pyridine or in the pyridine nucleus of quinoline did not react with dithioformic acid.

Dithioformic acid and secondary amines.

It has been shown by Todd, Bergel, Karimullah and Keller (J., 1937, in the press) that aliphatic secondary amines such as dimethylamine, diethylamine and piperidine or their hydrochlorides give with dithioformic acid the thioformyl derivatives. These were obtained as yellow liquids having the properties recorded by Willstätter and Wirth (Ber., 1909, 42, 1920). No reaction takes place, however, between dithioformic acid or its potassium salt and wholly or partly/

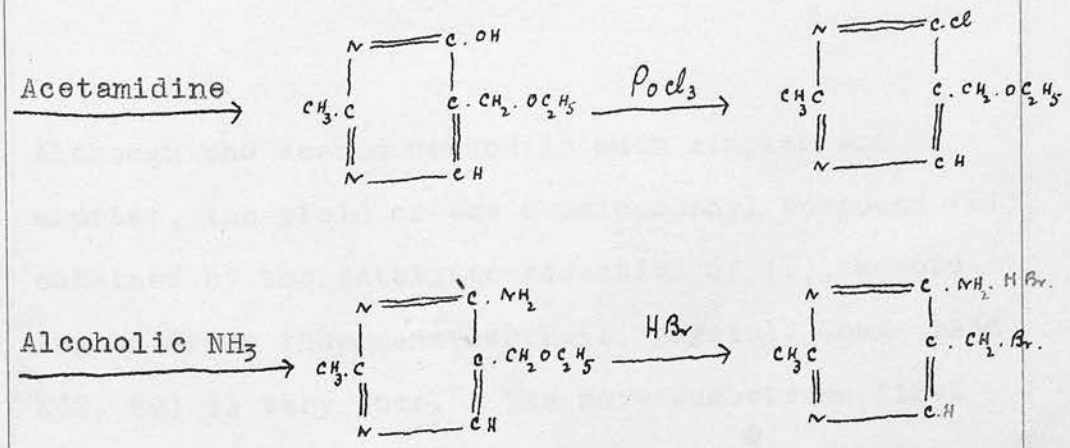
partly aromatic secondary amines. The following compounds were tried without result:

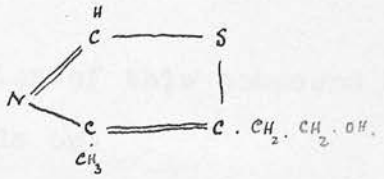
1. Diphenylamine
2. Methyl-aniline
3. Indole
4. Skatole

Action of formaldehyde on pyrimidines.

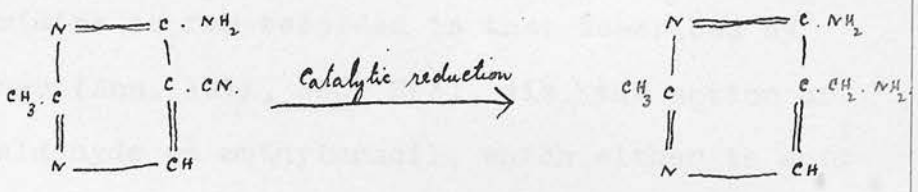
The two methods of synthesising aneurine so far reported are due to Williams and Cline (loc. cit.) and Todd and Bergel (loc. cit.). The former workers effected the synthesis by the following route:

$$C_2H_5O.CO.CH_2.CH_2.OC_2H_5 \xrightarrow{HCOOC_2H_5} C_2H_5O.CO.\underset{\underset{O=CH}{|}}{CH}.CH_2OC_2H_5$$

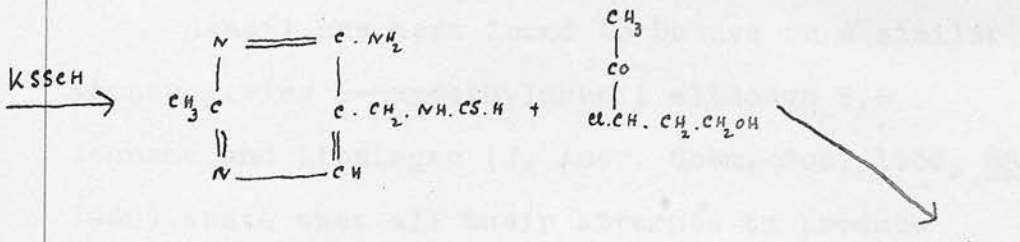


condensed with 

to give the vitamin B_1, whereas the latter workers synthesised it according to the scheme described already for the synthesis of quaternary thiazolium salts, viz.:

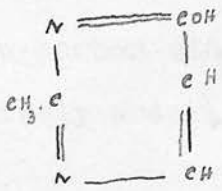


I. II.



Although the second method is much simpler and shorter, the yield of the 5-aminomethyl compound (II), obtained by the catalytic reduction of (I), according to Grewe (Hoppe-Seyler Zeit. physiol. Chem. 1936, 242, 89) is very poor. The more cumbersome first method involves the use of 5-oxymethyl-2-methyl-6-oxypyrimidine and it was thought of interest to attempt/

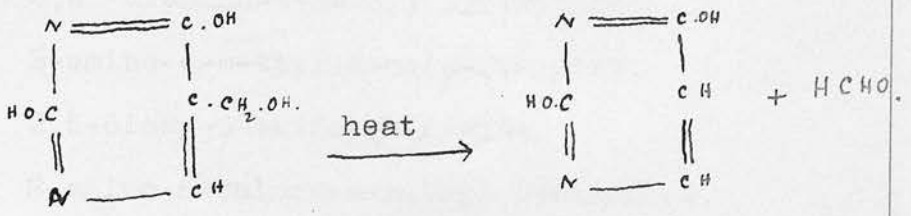
attempt the preparation of this compound by the action of formaldehyde on:



The only example of the action of formaldehyde on pyrimidine so far recorded is that described by Kircher (Ann. 1911, 385, 293), viz. the action of formaldehyde on methyluracil, which either in acid or in alkaline solution gives 5-oxymethyl-methyl uracil in good yield.

Uracil has been found to behave in a similar manner giving 5-oxymethyluracil although T.B. Johnson and Litzinger (J. Amer. Chem. Soc. 1936, 58, 1940) state that all their attempts to produce thyminyl alcohol by the action of formaldehyde on uracil have proved unsuccessful. The reason for their failure seems to be that whereas the sodium salt of 5-oxymethyl-methyluracil, being sparingly soluble in water, comes down crystalline from formaline solution, the salt of 5-oxymethyluracil is more soluble. It cannot be obtained by concentrating the solution because of its instability/

instability observed also by Johnson and Litzinger (loc. cit.) and Kircher (loc. cit.). On heating there is a carbon-carbon cleavage in position 5, giving quantitatively uracil and formaldehyde, thus:



If, however, a large volume of acetone is added, the sodium salt separates as an oily mass, which crystallises in course of time. On acidification with dilute acetic acid 5-oxymethyl uracil crystallises out.

Unfortunately formaldehyde has no similar action on 2-methyl-6-oxypyrimidine. By the procedure already described for 5-oxymethyl-uracil, the starting material or its sodium derivative was obtained. It remains to be seen whether the hydrogen atom in position 5 of the above pyrimidine is not sufficiently active and is activated only if an oxy-group is present in p-position to it, or whether an unstable 5-oxymethyl compound is formed and is cleaved again into 2-

methyl/

methyl-6-oxypyrimidine and formaldehyde.

The action of formaldehyde on the following pyrimidines was investigated, but in no case was the required 5-oxymethyl compound obtained:

1. 2,4-dimethyl-6-oxypyrimidine.
2. 2,6 -diamino-4-methyl pyrimidine.
3. 2-amino-4-methyl-6-oxypyrimidine.
4. 2,6-dioxy-6-aminopyrimidine.
5. 2-amino-6-chloro-4-methyl pyrimidine.
6. 2,4,6-trioxypyrimidine (barbituric acid)
7. 2-methyl 4,6-dioxy pyrimidine.
8. 2-methyl-6-amino pyrimidine.

Barbituric acid, 2-methyl-desoxy-barbituric acid and the amino pyrimidines listed above gave with formaldehyde amorphous products, which could not be characterised.

EXPERIMENTAL

N-methyl-2.4-dimethylthiazolium chloride.

Chloracetone (5 gm.) was heated on a water-bath to about 80°C. and N-methylthioacetamide (5 gm.) (prepared by heating N-methylacetamide with the required amount of P_2S_5 in benzene, m.p. 59°C. Yield 20%), added in small portions. On each addition a vigorous reaction took place. In the end the whole was a solid cake of crystals. It was dissolved in a little methyl alcohol (charcoal) and ether was added until a slight turbidity appeared. The chloride crystallised in colourless, very hygroscopic needles. m.p. 235°C. (decomp.). Yield almost quantitative. The substance was identical in every respect with that prepared from 2.4-dimethylthiazole and methyl iodide and transformed into chloride by means of AgCl.
(Found: Cl, 21.0. Calc. for $C_6H_{10}NSCl$, Cl, 21.7%)

N-phenyl /

N-phenyl-2.4-dimethylthiazolium chloride.

A mixture of thioacetanilide (5 gm.) and chloracetone (5.5 c.c.) was heated on the water-bath. After a few minutes a vigorous reaction ensued and the mass changed into a thick syrup. It was dissolved in about 30 c.c. water and treated with charcoal. 20% perchloric acid was added to the filtrate, whereupon N-phenyl-2.4-dimethylthiazolium perchlorate crystallised out in colourless needles. It was recrystallised from acetone-ether. m.p. 180°C. Yield quantitative.

(Found: C, 45.1; H, 4.5; N, 4.5. Calc. for $C_{11}H_{12}O_4NSCl$: C, 45.6; H, 4.1; N, 4.8%)

The chloride was prepared from the picrate (yellow needles, m.p. 115°C.) by dissolving it in 5% methyl alcoholic hydrochloric acid and precipitating with excess of ether. It was found to be very hygroscopic and showed a melting point of 184°C. (decomp.) in a sealed melting point tube. The iodide had all the characteristics recorded by Clarke and Gurin (J. Amer. Chem. Soc. 1935, 57, 1876).

S-acetonyl /

S-acetonyl-thioacetanilide hydrochloride.

Thioacetanilide (5 gm.) was added to chloracetone (6 c.c.) and the mixture allowed to stand at room temperature. After about 3 hours, crystals began to appear and in the course of the next half hour, the whole solidified. It was washed first with acetone and then with ether to remove the unchanged original material and crystallised from methyl alcohol-ether in colourless needles, m.p. 112°C. Yield quantitative.
(Found: C, 53.9; H, 5.8; N, 5.9; S, 13.0; Cl, 14.3; Calc. for $C_{11}H_{14}ONSCl$: C, 54.2; H, 5.8; S, 13.1; Cl, 14.6%).

The free base was obtained as an unstable oil, which decomposed when distilled, even in vacuum. The corresponding perchlorate melted at 130°C. A semi-carbazone was prepared from the hydrochloride, its melting point being 230°C. (decomp.). On heating the hydrochloride on the water-bath, it slowly changed into N-phenyl-2.4-dimethylthiazolium chloride.

Hydrolysis/

Hydrolysis of S-acetonyl-thioacetanilide.

The above hydrochloride was decomposed by boiling with water or dilute hydrochloric acid and oily drops appeared on the surface of the liquid. The whole was steam distilled. The distillate had an unpleasant odour like mercaptan and gave with $HgCl_2$ a white precipitate (m.p. 85°C.), containing sulphur.

A semi-carbazone was prepared from the distillate by heating it with semi-carbazide hydrochloride and sodium acetate and crystallised from methyl alcohol in colourless prisms, m.p. 213°C. (decomp.). The semi-carbazone showed a positive test for free SH group, i.e. a red coloration with a crystal of sodium nitrite in glacial acetic acid. $HgCl_2$ gave a white precipitate.
(Found: N, 19.4; S, 28.7. Calc. for $C_7H_{13}ON_3S_2$: N, 19.2; S, 29.2%).

The aqueous solution left after steam distillation was extracted with ether, which on evaporation gave a crystalline substance, identified as acetanilide (mixed m.p. 214-215°C.). The solution was then made alkaline and again extracted with/

with ether, on evaporation of which aniline was obtained (identified through its colour reactions and acetyl derivatives).

N-o-tolyl-2.4-dimethylthiazolium salts.

The thioacet-o-toluidine was prepared from acet-o-toluidine and P_2S_5 in the normal manner. m.p. 68°C. The condensation with chloracetone was effected exactly as described above for thioacetanilide. The perchlorate melted at 172°C. (Found: C, 47.7; H, 4.97; N, 4.5; Calc. for $C_{12}H_{14}O_4NSCl$ (perchlorate): C, 47.4; H, 4.6; N, 4.6%).

The picrate had a melting point of 150°C. and the iodide that of 217-218°C. with decomposition.

The corresponding intermediate product S-acetonyl-thioacet-o-toluidine was prepared in the same manner as its lower homologue. The hydrochloride melts at 125°C.
(Found: C, 55.95; H, 6.5; N, 5.6; Calc. for $C_{12}H_{16}ONSCl$: C, 55.9; H, 6.2; N, 5.4%).

It is more stable towards hydrolytic agents, but after a time gives toluidine, acet-o-toluidide and the above described sulphur containing component.

N /

N- o-nitrophenyl -2.4-dimethylthiazolium salts.

The o-nitro-thioacetanilide, necessary for this reaction, was prepared as follows:-

O-nitro-acetanilide (1 mol) and P_2S_5 (3.5 mols) were mixed intimately in a mortar and heated in portions of about 1 gm. each in test-tubes in the water-bath. (The heating should last not longer than 3 minutes, until the mass just begins to sinter; otherwise the mixture catches fire). The test-tubes were broken in a mortar and extracted with alcohol. The alcoholic solution was saturated with solid NaOH and after a time diluted with four times its volume of water. The precipitate obtained after passing CO_2 through this solution (charcoal) was dissolved again in 2% sodium hydroxide solution, whereby unchanged starting material remained undissolved. A nitro-thioacetanilide was precipitated almost pure by again passing CO_2 through the solution. It crystallised from acetone-water in yellow prisms, m.p. 114°C. (Found: C, 49.0; H, 4.3; N, 14.0. Calc. for $C_8H_8O_2N_2S$: C, 49.0; H, 4.1; N, 14.3%).

The thiazolium salts of this series were prepared/

prepared according to the methods given already. The perchlorate (m.p. 205°) crystallised from water in colourless plates.

(Found: C, 40.1; H, 3.5; N, 8.4; S, 9.3; Cl, 10.4. Calc. for $C_{11}H_{11}O_6N_2SCl$: C, 39.3; H, 3.6; N, 8.3; S, 9.5; Cl, 10.6%).

2:6-Diamino-5-thioformamido-4-methylpyrimidine.

2:5:6-Triamino-4-methylpyrimidine (Gabriel and Colman, B.34,1254) on treatment with potassium dithioformate in aqueous solution gave colourless needles (from water), m.p. 255° with evolution of hydrogen sulphide.

(Found: S, 17.2. $C_6H_9N_5S$ requires S, 17.5%).

3-(2':6'-Diamino-4'-methylpyrimidyl-5')-4-methyl-thiazolium chloride hydrochloride.

To a solution of the above thioformyl compound (1 mol.) in acetone, chloracetone (2 mols.) was added. The mixture was left for 3 days at room temperature, then diluted with an equal volume of alcohol, and refluxed for 4 hours. The colourless needles that separated were collected after cooling and recrystallised from alcohol-acetone/

acetone containing hydrogen chloride; needles, m.p. 315° (decomp.), were obtained containing water of crystallisation, which was only expelled with difficulty.

(Found: C, 31.2; H, 5.4; N, 19.9; S, 9.0; Cl, 20.4. $C_9H_{13}N_5Cl_2S.3H_2O$ requires C, 31.0; H, 5.5; N, 20.1; S, 9.2; Cl, 20.4%). The corresponding picrate has m.p. 255°. On shaking with alkaline potassium ferricyanide, a substance is produced which, though non-fluorescent in visible light, is blue-fluorescent in ultra-violet light; the fluorescence disappears when the liquid is made acid, but reappears when it is made alkaline again.

N-o-acetylaminophenyl-4-methylthiazolium chloride.

Mono-acetylphenylenediamine was prepared according to Leuchs (Ber., 1907, 40, 1084) but the tin was removed by hydrogen sulphide. Yield 58%.

Thioformyl-o-monoacetylphenylenediamine (5 gm.) was dissolved in acetone (300 c.c.) by heating and after cooling chloracetone (5 c.c.) was added. It was allowed to stand overnight at room temperature, subsequently refluxing it for 2 hours. After evaporation of the acetone, the residue was digested with ether to remove unchanged material/

material and crystallised from methanol-acetone (charcoal) in colourless plates, m.p. 222°C. Yield about 85%.
(Found: C, 53.8; H, 4.9; S, 11.5. Calc. for $C_{12}H_{13}ON_2SCl$: C, 53.6; H, 4.8; S, 11.9%).

In all these condensations acetone proved to be a useful solvent. In alcoholic solution the thioformyl group was often hydrolysed and 2-methylbenzimidazole was obtained instead of a thiazolium salt. The hydrochloride of the tertiary base got by treatment with dilute sodium hydroxide had 188° as its m.p.
(Found: C, 54.1; H, 4.9; S, 11.4; Cl, 13.43. Calc. for $C_{12}H_{13}ON_2SCl$: C, 53.6; H, 4.8; S, 11.9; Cl, 13.2%).

N-o-tolyl-4-methylthiazolium iodide prepared as above, from thioformyl o-toluidide (1 gm.) and chloracetone (1.2 gm.) in acetone (30 c.c.) was converted into the iodide by potassium iodide, m.p. 230°C (decomp.) from alcohol-ether. Yield 90%.
(Found: C, 42.1; H, 4.1; S, 9.6; Calc. for $C_{11}H_{12}NSI$: C, 41.7; H, 3.8; S, 10.0%).

N- /

N-benzyl-4-methylthiazolium chloride. Thioformyl-benzylamine condensed with chloracetone in equivalent amounts in the usual manner gave a salt which showed no depression in melting point when mixed with that obtained from benzyl chloride and 4-methylthiazole. m.p. 188°C.
(Found: N, 6.1. Calc. for $C_{11}H_{12}NSCl$: N, 6.2%).

Similarly N-o-nitro-benzyl-4-methylthiazolium chloride obtained from thioformyl o-nitro-benzylamine and chloracetone was identical with that from o-nitro-benzylchloride and 4-methylthiazole. m.p. 200°C.
(Found: N, 10.0. Calc. for $C_{11}H_{11}O_2N_2SCl$: N, 10.3%).

N-o-chlorobenzyl-4-methylthiazolium chloride.

o-Chlorbenzylchloride (3.5 gm.) was heated with 4-methylthiazole (2.5 gm.) on a water-bath for 2 hours. The crystalline mass was washed with ether and recrystallised from alcohol-ether, m.p. 190° (decomp.). Yield 4 gm.
(Found: C, 50.3; H, 4.5; Cl, 26.8. Calc. for $C_{11}H_{11}NSCl_2$: C, 50.7; H, 4.2; Cl, 27.3%).

2-o-chloro/

2-o-Chlorobenzylamino-4-methylthiazole hydrochloride, prepared from o-chlorbenzyl chloride and 2-amino-thiazole as above, crystallised from ethyl alcohol-ether in colourless needles, m.p. 260°C. (decomp.). The free base melted at 100°C. The hydrochloride and the free base show bluish-violet fluorescence in ultra-violet light.

(Found: C, 48.4; H, 4.5; Cl, 25.5. Calc. for $C_{11}H_{12}N_2SCl_2$: C, 48.0; H, 4.4; Cl, 25.8%).

2-o-Chlorobenzylamino-thiazole hydrochloride prepared from o-chlorobenzyl chloride and 2-amino-thiazole had a m.p. 245°C. m.p. of the free base being 58°C.

(Found: C, 46.3; H, 3.9. Calc. for $C_{10}H_{10}N_2SCl_2$: C, 46.0; H, 3.8%).

N-o-aminobenzyl-4-methylthiazolium chloride.

Hydriodic acid (sp. gr. 1.7, 8 c.c.) and red phosphorus (0.5 gm.) were heated nearly to boiling. After removing the flame N-o-nitrobenzyl-4-methyl-thiazolium chloride (1.5 gm.) was added in portions. On each addition a slight reaction ensued. In order to complete the reaction the whole was then boiled for half an hour. On cooling the crystalline mass was filtered through a glass filter and re-crystallised from water containing a little hydriodic acid/

acid, m.p. 237°.(decomp.). The crystals assume a brownish-yellow colour on exposure to light. The salt hydrolyses readily and by each successive recrystallisation the m.p. is lowered and the iodine content also falls. (Found: I, 54.6. Calc. for $C_{11}H_{14}N_2SI_2$: I, 55.2%)

The chloride was found to be more stable and was prepared by shaking the iodide with freshly precipitated silver chloride in methanol for 4 hrs. The filtrate was treated with excess of dry ether, the chloride crystallising in colourless needles, m.p. 213°(decomp.). (Found: N, 9.9; Cl, 25.7. Calc. for $C_{11}H_{14}N_2SCl_2$: N, 10.1; Cl, 25.7%).

General Methods for Thioformylation of Amines.

I. For amines insoluble or sparingly soluble in water.

The amine dissolved in ether or chloroform is shaken with a slight excess of potassium dithioformate. On evaporating organic solvent the thioformyl product separates. Alternatively the whole operation may be carried out in aqueous-alcoholic solution and the product precipitated by addition of water.

II. For amines soluble in water. An aqueous solution of amine or one of its salts is mixed with excess of potassium dithioformate solution; the derivative/

derivative separates on standing.

III. For amines giving water soluble thioformyl derivatives it is generally more convenient to shake together the amino and dithioformic acid in ether or dioxan solution till evolution of hydrogen sulphide ceases and then remove the solvent by distillation. Alternatively the amino hydrochloride and potassium dithioformate are shaken together in absolute alcohol.

Examples of Method I. Aniline (9.3 gm.) dissolved in alcohol (20 c.c.) was added to a solution of potassium dithioformate (12 gm.) in water (20 c.c.). After a short time separation of thioformanilide began, and was completed in 2 hours. Water was added and the crystalline product collected and recrystallised from hot water. Yield quantitative.

Using the same method thioform-o-toluidide m.p. 97°, was obtained from o-toluidine.

6-Amino-quinoline. To a solution of potassium dithioformate (1.5 gm.) in water (25 c.c.) was added 6-aminoquinoline (1 gm.) dissolved in chloroform and the mixture was shaken for a few minutes/

minutes. By bubbling nitrogen through the mixture the chloroform gradually evaporated leaving the thioformyl derivative suspended in the aqueous solution; it crystallised from acetone-petroleum ether in faintly yellow needles, m.p. 236°. (Found: S, 16.6. $C_{10}H N_2S$ requires S, 17.0). Yield quantitative.

Examples of Method II.

5-Amino-pyrimidines.

Tryptamine. To tryptamine (500 mg.) dissolved in water (80 c.c.) was added potassium dithioformate (400 mg.). After 15 minutes the solution became turbid and an oil separated which slowly crystallised. Recrystallised from petroleum ether (b.p. 60-80°) the product formed large plates m.p. 82°. (Found: S, 15.1; N, 13.7. $C_{11}H_{12}N_2S$ requires S, 15.7; N, 13.7).

Mezcaline. Mezcaline sulphate (200 mg.) and potassium dithioformate (150 mg.) in water (20 c.c.) deposited after 20 minutes an oil which slowly crystallised.

crystallised. The product separated from acetone-petroleum ether as colourless prisms, m.p. 92°. (Found: N, 5.7; S, 12.2. $C_{12}H_{17}O_3NS$ requires N, 5.5; S, 12.5). Yield quantitative.

o-Phenylenediamine.

Aqueous solutions of the amine gave with potassium dithioformate at 0° an unstable thioformyl derivative m.p. 77° which even at room temperature changed rapidly into benzimidazole, m.p. 170°. At temperatures above 0° the sole product was benzimidazole.

Mono-acetyl-o-phenylenediamine.

The thioformyl derivative crystallised from acetone-petroleum ether in colourless needles, m.p. 173°.
(Found: C, 55.7; H, 5.3; S, 16.3. $C_9H_{10}ON_2S$ requires C, 55.7; H, 5.1; S, 16.4). Yield quantitative.

Benzylamine /

Benzylamine.

Thioformyl derivative, m.p. 64°.

(Found: S, 20.7; C_8H_9NS requires S, 21.2).

o-Nitrobenzylamine.

Thioformyl derivative. m.p. 94°.

(Found: S, 15.9; $C_8H_8O_2N_2S$ requires S, 16.3).

o-Aminobenzylamine.

The amine reacted readily with potassium dithioformate in aqueous solution even at room temperature to give dihydroquinazoline, m.p. 128-129° in quantitative yield.

Thioformylation of glycine ester and condensation of the thioformyl derivative with chloracetone.

Glycine ester hydrochloride (1 gm.) and potassium dithioformate (1 gm.) were dissolved separately in water (10 c.c. each) and the solutions after being filtered from suspended impurities were mixed together. In about 10 minutes the mixture became turbid and hydrogen sulphide was evolved. In course of time oily drops appeared and after about 4 hours the mixture was repeatedly extracted with ether. The ether extract/

extract was dried with sodium sulphate and condensed with chloracetone in the usual way. After evaporation of the solvent, the oily residue crystallised from alcohol-ether (charcoal) in colourless plates. Yield approximately 85%. m.p. 236° (decomp.).

The presence of a free carboxyl group in the quaternary salt was shown by the fact that it turned blue litmus red and gave effervescence with sodium carbonate solution. This was also supported by analysis.

Analysis

4.236 mg. subst. gave 5.86 mg. CO_2 ; 1.62 mg. H_2O

7.191 mg. 8.255 mg. $BaSO_4$

(Found: C, 37.7; H, 4.28; S, 15.8.

$C_6H_8O_2NSCl$ requires C, 37.2; H, 4.12; S, 16.5%)

8-Thioformylamino quinoline.

Air was bubbled through a mixture of 8-amino quinoline (500 mg.) in chloroform and potassium dithioformate (700 mg.) in water for 2 days. Loss of chloroform through evaporation was made up from time to time. On the third day the greyish colour of aminoquinoline was changed to a distinct yellow. The/

The solid was filtered, dried and recrystallised from acetone-petrol ether. Slightly yellowish tinged needles, m.p. 112°C. Yield quantitative.

Analysis

4.714 mg. subst. gave 5.770 $BaSO_4$

Found: S, 16.8.

$C_{10}H_8N_2S$ requires S, 17.01%.

5-Thioformylamino-quinoline. was prepared in a similar manner. It crystallised from acetone-petrol ether in golden yellow needles. It was less soluble in petrol ether and acetone than the above compound.

Found: S, 16.6.

$C_{10}H_8N_2S$ requires S, 17.01.

2 and 3-aminoquinolines did not react with potassium dithioformate.

5-Oxymethyl-uracil.

Uracil (1 gm.) was dissolved in 5% sodium hydroxide/

hydroxide (7 c.c.) by warming and formaline 40% (2.5 c.c.) added. It was allowed to stand at room temperature for 24 hours. On addition of acetone (100 c.c.) the sodium salt of 5-oxymethyl uracil separated as an oil. This solidified after a time especially if washed often with acetone. It was dissolved in a little dilute acetic acid by warming and on scratching with glass rod 5-oxymethyl uracil crystallised in colourless needles. When recrystallised from water, it sintered at 205°C., decomposing with effervescence at 355°C.

Analysis

3.451 mg. subst. gave 5.250 mg. CO_2, 1.285 mg. H_2O

3.158 mg. " 0.528 c.c. N_2 20/758 mm.

Found: C, 41.5; H, 4.2; N, 19.4.

$C_5H_6O_3N_2$ requires C, 42.2; H, 4.2; N, 19.7.

The author wishes to thank Professor Barger for his advice and for his interest in the work.

A. R. TODD, F. BERGEL und KARIMULLAH

Über Aneurin, II. Mitteil.: Über die Synthese von *N*-Aryl-thiazoliumsalzen; über Einzelheiten in der Konstitution des Aneurins und Thiochroms

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SONDERABDRUCK AUS:
BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT

VERLAG CHEMIE G. M. B. H.
BERLIN

38. A. R. Todd[1]), F. Bergel und Karimullah: Über Aneurin[1a]), II. Mitteil.: Über die Synthese von *N*-Aryl-thiazoliumsalzen; über Einzelheiten in der Konstitution des Aneurins und Thiochroms.

[Aus d. Medizin.-chem. Institut d. Universität Edinburgh.]
(Eingegangen am 21. Dezember 1935.)

a) Über die Synthese von *N*-Aryl-thiazoliumsalzen: Wir aben bereits im ersten Teil[2]) unserer Abhandlungen über die Chemie des itamins B_1 (Aneurin) angedeutet, daß kürzlich H. T. Clarke und Gurin[3]) in ihrer Veröffentlichung über die Synthese des Thiazol-Spalticks aus Aneurin u. a. eine Methode zur Darstellung von *N*-Phenyliazoliumsalzen erwähnen, die wir unabhängig von ihnen ebenfalls geiden haben, wobei unsere Resultate die der amerikanischen Autoren um iges erweitern. Da diese Methode für die synthetische Seite des Vitaminoblems von einiger Bedeutung sein dürfte, möchten wir an der Hand von idell-Beispielen die Einzelheiten bekanntgeben.

N-Alkyl-thiazoliumsalze, auch die Benzylverbindung, lassen u leicht durch direkte Einwirkung von Alkylhalogeniden auf Thiazol-

[1]) Beit Memorial Research Fellow.

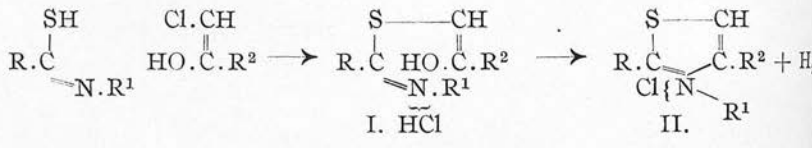
[1a]) Durch einen bedauerlichen Irrtum wurde in der vorhergehenden Veröffentung der Name „Antineurin" für das Vitamin B_1 verwendet. Inzwischen hat uns Prof. Jansen freundlichst darauf aufmerksam gemacht, daß sein Vorschlag „Aneulautete. Um Mißverständnisse zu vermeiden, soll von nun an dieser Name für das min B_1 gebräuchlich werden.

[2]) B. **68**, 2257 [1935].

[3]) Journ. Amer. chem. Soc. **57**, 1876 [1935].

Derivate darstellen. Alle Bestrebungen jedoch, die analogen *N*-Aryl-Verbindungen auf gleichem Wege aus halogenierten Benzol-Derivaten zu erhalten, schlugen fehl. Dieselben negativen Ergebnisse zeigten in 5-Stellung halogenierte Pyrimidine.

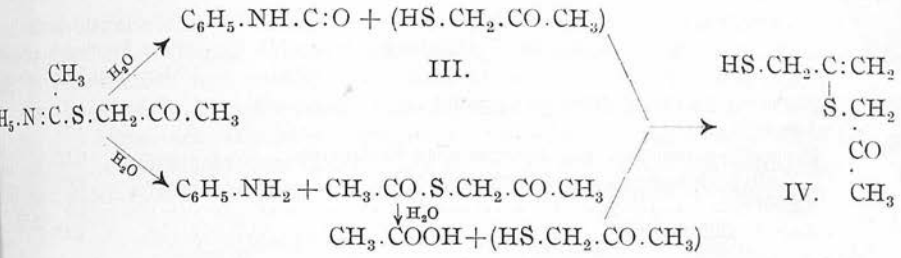
Es wurde als nächstes versucht, die wohlbekannte Hantzschsche Synthese von Thiazolen so zu modifizieren, daß sie zur Darstellung quartärer Thiazoliumsalze führen mußte. Es schien von vornherein nicht unmöglich, daß der Ersatz unsubstituierter Thio-amide in der Hantzsch schen Synthese durch Thio-amide von der allgemeinen Formel R.CS.NH.R^1 nach folgendem Schema zur Bildung der gewünschten Thiazoliumsalze führen könnte:



Diese Voraussetzung stellte sich als richtig heraus; die Reaktion ist ganz allgemein anwendbar.

In einem Vorversuch wurden *N*-Methyl-thioacetamid und Chloraceton zusammengebracht, wobei bereits in der Kälte, rascher in der Wärme, in beinahe quantitativer Ausbeute *N*-Methyl-2.4-dimethyl-thiazoliumchlorid (II, R = R^1 = R^2 = CH_3) gebildet wurde. Es wurde in das Jodid verwandelt und mit einem auf dem üblichen direkten Weg dargestellten Produkt identifiziert. Bei diesem Versuche konnte kein Zwischenprodukt, das der Formel I entsprochen hätte, gefaßt werden.

Verwendete man Thio-acetanilid und erhitzte es mit Chlor-aceton auf dem Wasserbade, mit oder ohne Alkohol als Lösungsmittel, so entstand direkt *N*-Phenyl-2.4-dimethyl-thiazoliumchlorid (II, R = R^2 = CH_3; R^1 = C_6H_5). Ließ man dagegen die Reaktion bei 15—20° verlaufen, so erhielt man eine unbeständige krystalline Substanz, die aber durch kurzes Erhitzen in das entsprechende Thiazoliumsalz verwandelt werden konnte. Die Vermutung, daß in diesem Produkt das Hydrochlorid des *S*-Acetyl-thioacetanilids (I, R = R^2 = CH_3; R^1 = C_6H_5) vorliegt, wurde durch Analyse und das Verhalten bei der hydrolytischen Spaltung bestätigt. In Wasser oder verd. Mineralsäuren unterliegt nämlich die Substanz, langsam in der Kälte, rascher beim Erhitzen, einer Hydrolyse, die unter Bildung von Anilin, Acetanilid und einer schwefel-haltigen Verbindung, die durch Kondensation eines hypothetischen Thiol-acetons (III) entstanden sein muß, vor sich geht. Da letztere ein Semicarbazon bildet, mit $HgCl_2$ einen farbigen Niederschlag gibt und Reaktionen auf eine SH-Gruppe liefert, ist sie vielleicht der Analyse nach, entsprechend Formel IV aufzufassen. Das Auftreten von Acetanilid unter den Endprodukten der Spaltung zeigt, daß der Zerfall interessanterweise nicht nur zwischen N und C, sondern auch zwischen C und S erfolgt:

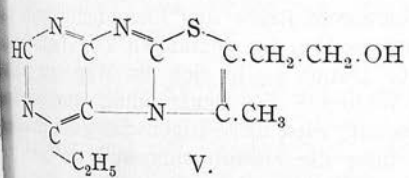


Kondensation von Chlor-aceton mit Thioacet-*o*-toluidid und *o*-Nitro-thioacetanilid führt zu *N*-*o*-Tolyl- bzw. *N*-*o*-Nitrophenyl-2.4-dimethyl-thiazoliumchlorid. Auch hierbei konnten die entsprechenden Zwischenprodukte gefaßt werden.

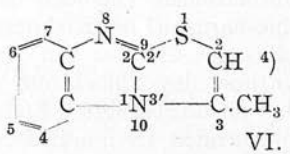
Die quartären Thiazoliumchloride konnten sämtlich isoliert werden, doch ist es angesichts ihrer großen Hygroskopizität besser, zur Isolierung die Jodide und besonders die Perchlorate zu verwenden.

Nähere Angaben über die Darstellung der entsprechenden Pyrimidin-Derivate erfolgen später. Die Synthese der als Ausgangsmaterial nötigen, bisher unbekannten 5-Thioacyl-amino-pyrimidine ist mit gewissen Schwierigkeiten verbunden.

b) Über Einzelheiten in der Konstitution des Aneurins und Thiochroms: In unserer ersten Veröffentlichung[2]) haben wir vor kurzem Formel V für das Thiochrom vorgeschlagen. Seit der Einsendung



V.



VI.

dieser Arbeit haben A. Windaus, R. Tschesche und R. Grewe[5]) und in einer anderen Veröffentlichung R. Kuhn und H. Vetter[6]) eine ähnliche Formulierung vertreten. Sie unterscheidet sich nur dadurch von der unsrigen, daß im Pyrimidin-Teil in 2- und 4-Stellung Methylgruppen angenommen werden, während unser Ringsystem in 4-Stellung nur eine Äthylgruppe (wie auch in der Williamsschen Formulierung vorgesehen ist) trägt. Während Windaus und Mitarbeiter ihre theoretische Auffassung vom Thiochrom von der noch nicht endgültig geklärten Konstitution der von ihnen durch Salpetersäure bezw. Bariumpermanganat erhaltenen Pyrimidin-Spaltstücke (a. a. O.) ableiten, stützt Kuhn seine Auffassung auf die Ergebnisse seiner *C*-Methyl-Bestimmungen[7]).

Zur Klärung der Natur und Zahl der Alkylgruppen im Aneurin und Thiochrom haben wir schon vor einiger Zeit Bestimmungen der *C*-ständigen Alkylgruppen von einer Reihe von Substanzen, die in folgender Tabelle vereinigt sind, durchführen lassen[8]):

[4]) Bezifferung gemäß den Vorschlägen in Band III d. Literatur-Register d. Organ. Chemie. [5]) Ztschr. physiol. Chem. **237**, 98 [1935]. [6]) B. **68**, 2375 [1935].
[7]) B. 68, 2383 [1935]. [8]) Bestimmungen von Hrn. Dr. H. Roth (Heidelberg).

Name der Verbindung	Durchschnitt der Äquivalente Säure bezog. auf Essigsäure
N-Phenyl-2.4-dimethyl-thiazoliumjodid	1.31
5-Methyl-uracil	0.77
Pyrimidin-sulfonsäure aus Aneurin nach Williams	0.62
3-Methyl-[thiazolo-2′. 3′:2. 1-benzimidazol]	1.0
Thiochrom	1.6
Aneurin-Chlorhydrat	1.35

Zieht man angesichts dieser Tabelle in Betracht, daß für eine Alk gruppe, und dies kann unserer Meinung nach auch eine Äthylgruppe se der Äquivalentwert zwischen 0.62 und 1 schwankt, so ergibt sich dara daß 1) Williams Pyrimidin-Spaltstück nur eine Alkylgruppe, d. h. e Äthylgruppe, besitzt, 2) Thiochrom und Aneurin die gleiche Zahl v Alkylgruppen, nämlich zwei, haben, 3) der höhere Wert beim Thioch gegenüber dem Aneurin (Kuhn[9]) errechnet überraschenderweise 1.75 Äq valente) gedeckt ist, durch die Tatsache, daß die von uns dargestellte V bindung 3-Methyl-[thiazolo-benzimidazol] (siehe weiter unten) das *C*-Met quantitativ abspaltet; es ist in seiner Konstitution analog der vorgeschlage Thiochrom-Formel; dagegen gibt das, wie das Aneurin, quartäre T zoliumsalz verminderte Ausbeuten.

Uns scheint nach diesen Überlegungen die Formulierung nach Willia mit einem Äthyl-pyrimidin die bevorzugte zu sein.

Das soeben erwähnte Thiazolo-benzimidazol wurde im Verlauf uns synthetischen Versuche in der Thiochrom-Reihe aus Pheuylendiamin Thio-harnstoff bei nachheriger Kondensation des gebildeten Thio-benzim zolins mit Chlor-aceton, dargestellt. Damit ergibt sich ein Weg zur T synthese des Thiochroms selbst. Während das Benzprodukt nur schw blau im ultravioletten Licht fluoresciert, wird diese Eigenschaft bei den sprechenden Pyrimidin-Derivaten, über die zusammenfassend zu beric sein wird, immer deutlicher.

Für finanzielle Unterstützung durch die Rockefeller-Stiftung möc wir auch an dieser Stelle unseren Dank aussprechen.

Beschreibung der Versuche.

N-Benzyl-2.4-dimethyl-thiazoliumbromid.

Äquimolekulare Mengen von Benzylbromid und 2.4-Dime thiazol wurden 15 Min. auf dem Wasserbade erwärmt. Der entsta Krystallbrei wurde mit Äther gewaschen und aus Alkohol-Äther umkry siert. Schmp. 173°.

3.683 mg Sbst.: 0.156 ccm N (10°, 747 mm).

$C_{12}H_{14}NSBr$. Ber. N 4.9. Gef. N 5.0.

N-Methyl-2.4-dimethyl-thiazoliumchlorid.

Das für die Umsetzung nötige *N*-Methyl-thioacetamid wur *N*-Methyl-acetamid durch Erhitzen mit P_2S_5 in Benzol dargestellt 59°, Ausbeute 20% d. Th.). 5 ccm Chlor-aceton wurden auf dem

[9]) a. a. O.

bade auf 80° erwärmt und 5 g *N*-Methyl-thioacetamid in kleinen Portionen hinzugefügt. Es erfolgte jedesmal eine heftige Reaktion, wobei am Ende die Reaktionsmasse fest wurde. Sie wurde in wenig Methylalkohol gelöst und mit Äther bis zur beginnenden Trübung versetzt. Beim Stehen krystallisierte das Chlorid aus. Farblose, sehr hygroskopische Nadeln, Schmp. 235° unt. Zers. Ausbeute fast quantitativ. Die Substanz erwies sich als identisch mit dem aus 2.4-Dimethyl-thiazol-Methyljodid mit Silberchlorid dargestellten Cl-Salz.

$C_6H_{10}NSCl$. Ber. Cl 21.7. Gef. Cl 21.0.

N-Phenyl-2.4-dimethyl-thiazoliumsalze.

Eine Mischung von 5 g Thio-acetanilid und 5.5 ccm Chlor-aceton wurde auf dem Wasserbade unter Ausschluß von Feuchtigkeit erhitzt. Nach einigen Minuten trat eine heftige Reaktion ein, und das Gemisch verwandelte sich in einen zähen Sirup. Dieser wurde in 25—30 ccm Wasser gelöst, mit Tierkohle behandelt und filtriert. Auf Zusatz einer 20-proz. Lösung von Überchlorsäure fiel das *N*-Phenyl-2.4 dimethyl-thiazoliumperchlorat in farblosen Nadeln aus. Aus Aceton-Äther umkrystallisiert, zeigte es einen Schmp. von 180°. Ausbeute quantitativ.

$C_{11}H_{12}O_4NSCl$. Ber. C 45.6, H 4.1, N 4.8.
Gef. „ 45.1, „ 4.5, „ 4.5.

Das Pikrat bildete gelbe Nädelchen, die bei 115° schmolzen. Das Chlorid wurde in farblosen Nadeln erhalten, wenn man das Pikrat in 5-proz. methylalkohol. Salzsäure löste und mit Äther fällte. Es ist außerordentlich hygroskopisch und schmilzt im geschlossenen Röhrchen bei 184° unt. Zers. Das Jodid hatte die von Clarke und Gurin[3]) angegebenen Eigenschaften.

S-Acetonyl-thioacetanilid-Hydrochlorid.

Zu 6 ccm Chlor-aceton wurden 5 g Thio-acetanilid bei 15—20° hinzugefügt und das Gemisch sich selbst überlassen. Nach etwa 3 Stdn. begannen sich plötzlich Krystalle auszuscheiden, und nach weiteren 30 Min. war der Kolben-Inhalt eine feste Masse geworden. Das Produkt wurde zuerst mit Aceton und dann mit Äther zur Entfernung von unverändertem Chloraceton gewaschen und aus Methylalkohol-Äther umkrystallisiert. Das so gewonnene *S*-Acetonyl-thioacetanilid-Hydrochlorid bildete farblose Nädelchen und schmolz bei 112°. Ausbeute fast quantitativ.

Die freie Base wurde als unbeständiges Öl, das sich selbst bei Vakuum-Destillation zersetzte, erhalten. Das entsprechende Perchlorat schmolz bei 130°. Außerdem ließ sich ein Semicarbazon aus dem Hydrochlorid darstellen, das bei 230° unt. Zers. schmolz. Beim Erwärmen auf dem Wasserbade ging das Chlorid langsam in das *N*-Phenyl-2.4-dimethyl-thiazoliumchlorid über.

$C_{11}H_{14}ONSCl$. Ber. C 54.2, H 5.8, N 5.8, S 13.1, Cl 14.6.
Gef. „ 53.9, „ 5.8, „ 5.9, „ 13.0, „ 14.3.

Hydrolyse des *S*-Acetonyl-thioacetanilids: Das oben erwähnte Chlorid zersetzte sich beim Kochen mit Wasser oder verd. Salzsäure unter Bildung von öligen Tröpfchen. Das Reaktionsgemisch wurde einer Destillation mit Wasserdampf unterworfen. Das Destillat hatte einen mercaptan-ähnlichen, unangenehmen Geruch und gab mit $HgCl_2$ eine weiße Fällung (Schmp. 85°), die Schwefel enthielt. Beim Erwärmen der ursprünglichen wäßrigen Lösung

mit Semicarbazid-Chlorhydrat und Natriumacetat fiel ein Semicarbazo aus, das aus Methylalkohol in farblosen Prismen krystallisierte. Schmp. 21 unt. Zers. Das Semicarbazon gab positive Reaktionen auf freies SH; so en stand Rotfärbung mit einem Körnchen Natriumnitrit in Eisessig, und Queck silberchlorid verursachte eine weiße Fällung.

3.874 mg Sbst.: 8.100 mg $BaSO_4$. — 3.563 mg Sbst.: 0.592 ccm N (13°, 744 mm
$C_7H_{13}ON_3S_2$. Ber. N 19.2, S 29.2.
Gef. „ 19.4, „ 28.7.

Aus dem Rückstand von der Wasserdampf-Destillation wurde durc Äther-Extraktion eine krystalline Substanz isoliert, die sich als Acetanili herausstellte (Misch-Schmp. 114—115°). Der wäßrige Rest wurde alkalis gemacht und mit Äther extrahiert. Der Äther-Extrakt enthielt Anili (durch sein Acetylderivat identifiziert).

N-*o*-Tolyl-2.4-dimethyl-thiazoliumsalze.

Das für die Umsetzung nötige Thioacet-*o*-toluidid wurde aus Ac *o*-toluidid mittels P_2S_5 gewonnen; Schmp. 68°. Die Kondensation mit Chlo aceton folgte in den Grundzügen den beim Thio-acetanilid beschrieben Einzelheiten. Das Perchlorat schmilzt bei 172°, das Pikrat bei 150° u das Jodid bei 217—218° unt. Zers.

$C_{12}H_{14}O_4NSCl$ (Perchlorat). Ber. C 47.4, H 4.6, N 4.6.
Gef. „ 47.7, „ 4.97, „ 4.5.

Das entsprechende Zwischenprodukt *S*-Acetonyl-thioacet-*o*-tol did wurde in gleicher Weise wie das niedrige Homologe dargestellt. Hydrochlorid (Schmp. 125°) ist stabiler gegen hydrolytische Einflüs gibt aber nach einiger Zeit Toluidin, Acet-*o*-toluidid und dieselbe schw felhaltige Komponente, die oben beschrieben ist.

3.271 mg Sbst.: 6.710 mg CO_2, 1.910 mg H_2O. — 3.938 mg Sbst.: 0.102 cc (18.5°, 744 mm).
$C_{12}H_{16}ONSCl$. Ber. C 55.9, H 6.2, N 5.4.
Gef. „ 55.95, „ 6.5, „ 5.6.

N-[*o*-Nitro-phenyl]-2.4-dimethyl-thiazoliumsalze.

Das für die Umsetzung nötige *o*-Nitro-thioacetanilid wurde folgt dargestellt: 1 Mol. *o*-Nitro-acetanilid wurde mit 3.5 Mol. Ph phorpentasulfid in einem Mörser innig gemischt und in Portionen etwa 1 g in einem Reagensglas im Wasserbade erhitzt. Das Erwärmen nicht länger als 3 Min. dauern, bis gerade die Schmelze zusammensi Andernfalls fängt das Gemisch Feuer. Die Reagensgläser werden in ei Mörser zerkleinert und die Masse aus Glas und Reaktionsprodukt mit Alk ausgezogen. Die Alkohol-Lösung wurde mit festem Ätznatron gesät stehen gelassen und nach einiger Zeit mit Wasser verdünnt. Hierauf w filtriert und mit gasförmigem CO_2 gefällt. Das entstandene Produkt w mit 2-proz. Natronlauge erneut zur Lösung gebracht, wobei unverände Ausgangsmaterial zurückblieb. Wiederum mit CO_2 gefällt, ließ sich *o*-Nitro-thioacetanilid aus Aceton-Wasser umkrystallisieren. Prismen, Schmp. 114°.

$C_8H_8O_2N_2S$. Ber. C 49.0, H 4.1, N 14.3.
Gef. „ 49.0, „ 4.3, „ 14.0.

Die Thiazoliumsalze dieser Reihe wurden auf dem bereits beschriebenen Wege bereitet. Perchlorat, Schmp. 205°, krystallisierbar aus Wasser, farblose Blättchen.

3.730 mg Sbst.: 5.49 mg CO_2, 1.17 mg H_2O. — 3.432 mg Sbst.: 0.250 ccm N (18°, 744 mm). — 4.511 mg Sbst.: 3.050 mg $BaSO_4$. — 3.851 mg Sbst.: 1.620 mg AgCl.

$C_{11}H_{11}O_6N_2SCl$. Ber. C 39.3, H 3.6, N 8.3, S 9.5, Cl 10.6.
Gef. „ 40.1, „ 3.5, „ 8.4, „ 9.3, „ 10.4.

C-Alkyl-Bestimmungen.

Bei der Oxydation mit Chromsäure nach R. Kuhn und H. Roth wurde gefunden:

a) 7.457 mg, 6.841 mg *N*-Phenyl-2.4-dimethyl-thiazoliumjodid: 3.09, 2.85 ccm $n/_{100}$-NaOH.

$C_{11}H_{12}NSJ$. Gef. Äquiv. Essigsäure 1.31, 1.32.

b) 6.848, 7.190 mg 5-Methyl-uracil: 4.26, 4.34 ccm $n/_{100}$-NaOH.

$C_5H_6O_2N_2$. Gef. Äquiv. Essigsäure 0.78, 0.76.

c) 5.766, 4.981 mg Pyrimidin-sulfonsäure aus Aneurin: 1.78, 1.51 ccm $n/_{100}$-NaOH.

$C_6H_9O_3N_3S$. Gef. Äquiv. Essigsäure 0.63, 0.62.

d) 8.273, 7.180 mg 3-Methyl-[thiazolo-benzimidazol]: 4.50, 3.85 ccm $n/_{100}$-NaOH.

$C_{10}H_8N_2S$. Gef. Äquiv. Essigsäure 1.02, 1.00.

e) 5.687 mg Thiochrom: 3.45 ccm $n/_{100}$-NaOH.

$C_{12}H_{14}ON_4S$. Gef. Äquiv. Essigsäure 1.59.

f) 7.120, 7.328 mg Aneurin-Chlorhydrat: 2.83, 2.96 ccm $n/_{100}$-NaOH.

$C_{12}H_{18}ON_4SCl_2$. Gef. Äquiv. Essigsäure 1.34, 1.36.

3-Methyl-[thiazolo-*2'.3'*:*2.1*-benzimidazol] (VI).

Ein Gemisch von 2 g *o*-Phenylendiamin und 1.4 g Thio-harnstoff wurde 1 Stde. auf 180° erhitzt. Unter starker Ammoniak-Entwicklung setzte sich das anfangs flüssige Gemenge zu einem Krystallbrei um, der etwas rötlich gefärbt war. Aus heißem Alkohol umgelöst, ergab sich Thio-benzimidazolin vom Schmp. 295—300°. Ausbeute 1.3 g.

1 g von letzterem wurde mit 0.6 g Chlor-aceton 3—5 Min. erwärmt. Es trat plötzliche Reaktion ein, unter Schmelzen des ganzen Gemisches und Wiederfestwerden. Das Produkt wurde in Wasser gelöst, mit Äther gewaschen und alkalisch gemacht. Der Niederschlag wurde aus verd. Alkohol umkrystallisiert; kleine, farblose Prismen, Schmp. 164—165°. Ausbeute 1 g. In alkohol. Lösung fluoresciert die Substanz im ultravioletten Licht schwach blau.

3.320 mg Sbst.: 7.780 mg CO_2, 1.290 mg H_2O. — 4.045 mg Sbst.: 0.516 ccm N (18°, 748 mm). — 4.422 mg Sbst.: 5.570 mg $BaSO_4$.

$C_{10}H_8N_2S$. Ber. C 63.8, H 4.3, N 14.9, S 17.0.
Gef. „ 63.9, „ 4.35, „ 14.9, „ 17.3.

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ANEURIN

PART III. METHYL α-CHLORO-γ-HYDROXYPROPYL KETONE AND ITS APPLICATION TO THIAZOLE SYNTHESIS

BY
A. R. TODD,
F. BERGEL,
AND
(Miss) A. JACOB

PART IV. 5-THIOFORMAMIDOPYRIMIDINES

BY
A. R. TODD,
F. BERGEL,
AND
KARIMULLAH

PART V. THE SYNTHESIS OF 3-PYRIMIDYLTHIAZOLIUM SALTS, INCLUDING AN ISOMER OF ANEURIN

BY
A. R. TODD
AND
F. BERGEL

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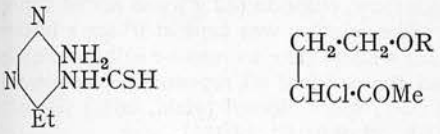
342. *Aneurin. Part III.* Methyl α-Chloro-γ-hydroxypropyl Ketone and its Application to Thiazole Synthesis.*

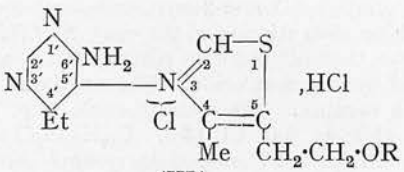
By A. R. Todd, F. Bergel, and (Miss) A. Jacob.

By cleavage of aneurin (vitamin B_1) with an acid solution of sodium sulphite Williams, Waterman, Keresztesy, and Buchman (*J. Amer. Chem. Soc.*, 1935, **57**, 536) obtained an acidic substance $C_6H_9O_3N_3S$, considered to be a pyrimidinesulphonic acid, and a base C_6H_9ONS, which Clarke and Gurin (*ibid.*, p. 1876) showed to be identical with 4-methyl-5-β-hydroxyethylthiazole. Largely on the basis of this work Williams (*ibid.*, p. 229) formulated the vitamin hydrochloride as 3-(6′-amino-4′-ethylpyrimidyl-5′)-4-methyl-5-β-hydroxyethylthiazolium chloride hydrochloride (III; R = H).



(I.)

(II.)



(III.)

It seemed possible that quaternary salts of type (III) might be synthesised by extending the methods employed for 3-arylthiazolium salts (Clarke and Gurin, *loc. cit.*; Todd, Bergel, and Karimullah, *Ber.*, 1936, **69**, 217) to the condensation of 6-amino-5-thioformamido-4-ethylpyrimidine (I) with a suitable α-halogenated ketone (II). In their synthesis of 4-methyl-5-β-hydroxyethylthiazole Clarke and Gurin (*loc. cit.*) condensed methyl α-chloro-γ-ethoxypropyl ketone (II; R = Et) with thioformamide and subsequently de-alkylated the 4-methyl-5-β-ethoxyethylthiazole initially formed, by heating in a sealed tube with concentrated hydrochloric acid. Such treatment is known to deaminate aneurin (Buchman and Williams, *J. Amer. Chem. Soc.*, 1935, **57**, 1751; Barger, Bergel, and Todd, *Ber.*, 1935, **68**, 2257), so the above-mentioned ethoxy-ketone was regarded as useless for our purpose.

We therefore synthesised *methyl α-chloro-γ-hydroxypropyl ketone* (II; R = H) according to the scheme :

$$CH_3{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2Br + CH_3{\cdot}CO{\cdot}CHNa{\cdot}CO_2Et \longrightarrow CH_3{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2Et){\cdot}CO{\cdot}CH_3 \quad (IV.)$$

$$\xrightarrow{SO_2Cl_2} \underset{(V.)}{CH_3{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CCl(CO_2Et){\cdot}CO{\cdot}CH_3} \xrightarrow{\text{dil. } H_2SO_4} HO{\cdot}CH_2{\cdot}CH_2{\cdot}CHCl{\cdot}CO{\cdot}CH_3$$

The condensation of β-bromoethyl acetate with ethyl sodioacetoacetate at 160° (Haller and March, *Compt. rend.*, 1908, **139**, 100; *Bull. Soc. chim.*, 1905, **33**, 618) is unsatisfactory; better results are obtained by using benzene as a diluent and refluxing the mixture on the water-bath. Chlorination of (IV) with sulphuryl chloride proceeds smoothly, and the desired chloro-ketone is obtained on careful hydrolysis of the product (V).

Methyl α-chloro-γ-hydroxypropyl ketone condensed readily with thioformamide, yielding 4-methyl-5-β-hydroxyethylthiazole, whose *picrate* gave no depression in m. p. when mixed with the specimen (m. p. 162°) prepared from the vitamin.

Efforts were also made to prepare methyl α-halogeno-γ-phenoxypropyl ketones in the hope that the phenoxythiazoles resulting from their condensation with thioamides would yield the corresponding hydroxy-compounds under relatively mild conditions. At first, direct halogenation of methyl γ-phenoxypropyl ketone (Boyd, Barrett, and Robinson, J., 1932, 318) was tried under a variety of conditions, but no homogeneous products could be isolated. The synthesis of *methyl α-chloro-γ-phenoxypropyl ketone* (II; R = Ph) was, however, effected by a method analogous to that employed for the corresponding hydroxy-compound (II; R = H); as is evident from the chlorine content, the substance could

* Part II; *Ber.*, 1936, **69**, 217.

not be purified completely, but condensation with thioacetamide gave in good yield, 2 : 4-dimethyl-5-β-phenoxyethylthiazole, isolated as its *picrate*. Further experiments with phenoxythiazoles were discontinued, as replacement of the phenoxy-group by hydroxyl could not be satisfactorily accomplished.

Experimental.

Ethyl α-2-Acetoxyethylacetoacetate (IV).—To a suspension of dry ethyl sodioacetoacetate (152 g.) in dry benzene (700 c.c.), β-bromoethyl acetate (167 g.) was added at 15—20°. The mixture was heated on the water-bath until the solution reacted faintly alkaline (6—10 hours), then cooled, poured into ice-water, and extracted with ether. After removal of the ether the residual oil was distilled under reduced pressure, the fraction, b. p. 138—142°/12 mm., being collected (yield, 25%). Haller and March (*loc. cit.*) give b. p. 147—150°/13 mm.

Ethyl α-Chloro-α-2-acetoxyethylacetoacetate (V).—Sulphuryl chloride (82 g.) was added during 1 hour with stirring to the ester (IV) (123 g.) at 0°. The solution was kept at 0° for a further hour, then diluted with ether (250 c.c.) and refluxed for a short time to remove sulphur dioxide and hydrogen chloride. The ether was removed, and the residual oil repeatedly fractionated in a vacuum. The main fraction, b. p. 120—121°/2 mm., was collected (yield, 86%) (Found: C, 47·9; H, 6·0; Cl, 13·3. $C_{10}H_{15}O_5Cl$ requires C, 47·9; H, 6·0; Cl, 14·1%).

Methyl α-Chloro-γ-acetoxypropyl Ketone (II; R = $CO{\cdot}CH_3$).—The above ester (V) was heated under reflux for 6 hours with a mixture of dilute sulphuric acid (20 c.c. of 15%) and glacial acetic acid (20 c.c.). The solution was cooled, poured into water, and extracted with ether. After removal of the ether and acetic acid a colourless liquid was obtained which after several fractionations boiled at 90—93/2 mm. (yield, 40%) (Found: C, 47·1; H, 6·2; Cl, 19·8. $C_7H_{11}O_3Cl$ requires C, 47·0; H, 6·2; Cl, 19·9%).

Methyl α-Chloro-γ-hydroxypropyl Ketone (II; R = H).—The chloro-ester (V) was heated under reflux during 4 hours with dilute sulphuric acid (35 c.c. of 35%) and alcohol (70 c.c.), then poured into water, and the mixture extracted with ether. On removal of ether from the dried extract an oil was left which after repeated fractionation gave a colourless liquid, b. p. 85—92°/16 mm. (yield, 20%) (Found: Cl, 25·4. $C_5H_9O_2Cl$ requires Cl, 26·0%).

4-*Methyl*-5-β-*hydroxyethylthiazole*.—An ethereal solution of thioformamide was prepared by shaking together finely powdered phosphorus pentasulphide (12 g.), formamide (20 g.), and absolute ether (200 c.c.) for *ca.* 20 hours (Gabriel, *Ber.*, 1916, **49**, 1145); the clear ethereal layer was decanted and used as a stock solution of thioformamide.

When a mixture of the chloro-ketone (II; R = H) (250 mg.) and the thioformamide solution (10 c.c.) was kept, colourless crystals of the thiazole hydrochloride slowly separated. After 5 hours the ether was distilled off, and the residue heated for 1 hour at 100°, cooled, and dissolved in dilute hydrochloric acid. After extraction with ether to remove any unchanged ketone, the solution was made strongly alkaline and again extracted with ether. The extract on evaporation yielded 4-methyl-5-β-hydroxyethylthiazole as an almost colourless oil, b. p. 250—255° (capillary method of Emich). The base was not purified further; treatment with ethereal picric acid gave a *picrate* crystallising from alcohol in yellow needles, m. p. 162—163° (Found: S, 8·2. $C_{12}H_{12}O_8N_4S$ requires S, 8·6%).

Ethyl α-2-Phenoxyethylacetoacetate.—This *ester* was prepared from β-phenoxyethyl bromide and ethyl sodioacetoacetate in alcoholic solution (cf. Boyd, Barrett, and Robinson, *loc. cit.*). It had b. p. 148°/4 mm. (Found: C, 68·1; H, 7·3. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

Ethyl α-Chloro-α-2-phenoxyethylacetoacetate.—The above ester (10 g.) was chlorinated with sulphuryl chloride (6 g.) in the manner described under the corresponding acetoxy-compound (V). The *product* was a colourless liquid, b. p. 135—140°/3 mm. (yield, 70%) (Found: C, 59·3; H, 6·1; Cl, 11·9. $C_{14}H_{17}O_4Cl$ requires C, 59·1; H, 6·0; Cl, 12·4%).

Methyl α-Chloro-γ-phenoxypropyl Ketone (II; R = Ph).—The above chloro-ester (7 g.) was hydrolysed by refluxing for 4 hours with a mixture of dilute sulphuric acid (14 c.c. of 15%) and glacial acetic acid (14 c.c.). After repeated distillation the main fraction of the product boiled at 168—172°/12 mm. (Found: C, 62·0; H, 6·0; Cl, 12·2. $C_{11}H_{13}O_2Cl$ requires C, 62·1; H, 6·1; Cl, 16·7%). The low chlorine content may be due to partial decomposition during distillation; that the substance is mainly the desired ketone is shown by its condensation with thioacetamide.

2 : 4-*Dimethyl*-5-β-*phenoxyethylthiazole*.—The above chloro-ketone (200 mg.) reacted rapidly with thioacetamide (60 mg.) when the mixture was warmed for a few minutes over a free flame. The free base was finally obtained as a colourless thick oil. It gave a *picrate* crystal-

lising from alcohol in yellow needles, m. p. 122° (Found: N, 12·1; S, 6·8. $C_{19}H_{18}O_8N_4S$ requires N, 12·1; S, 6·9%).

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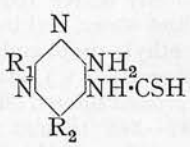
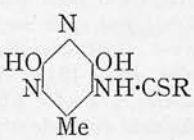
343. *Aneurin. Part IV. 5-Thioformamidopyrimidines.*

By A. R. Todd, F. Bergel, and Karimullah.

For the synthesis of 3-pyrimidylthiazolium salts according to the scheme indicated in the preceding paper it is necessary to synthesise 5-thioformamidopyrimidine derivatives including those of type (I). It is known that an amino-group in position 5 of the pyrimidine nucleus is unique in that it is readily acylated; amino-groups in other positions are not. Thus, formylation of a 5 : 6-diaminopyrimidine leads to the formation of the corresponding 6-amino-5-formamidopyrimidine and not to a diformyl derivative (Gabriel and Colman, *Ber.*, 1901, **34**, 1246; Johns, *Amer. Chem. J.*, 1908, **41**, 58). Thioacylamidopyrimidines are not described in the literature, and we were unable to prepare them by the action of phosphorus pentasulphide on the corresponding acyl derivatives. A similar lack of success was encountered on attempting to replace the 5-amino-group by an *iso*nitrile group with a view to subsequent addition of hydrogen sulphide according to Hofmann (*Ber.*, 1878, **11**, 339).

(I.) 

 (II.)

Thioacetic acid reacts readily with primary amines to give the corresponding acetyl derivatives (Pawlewski, *Ber.*, 1898, **31**, 661; 1902, **35**, 110); accordingly we next tried direct thioacylation by heating amines with dithio-acids (R·CS·SH). With dithioacetic acid, this was completely successful and 5-*thioacetamido*-4-*methyluracil* (II; R = Me) was readily obtained from 5-amino-4-methyluracil. Dithioformic acid acts in a similar way,* but the yield is not good and the product is difficult to purify. It was, however, found that the thioformylation can be readily effected by mixing aqueous solutions of 5-aminopyrimidines and potassium dithioformate; at room temperature in an atmosphere of carbon dioxide the thioformyl derivatives normally separate in almost pure condition, the yield being nearly quantitative. Amino-groups in positions 2, 4 and 6 of the pyrimidine nucleus did not react under these conditions.

In this way 6-*amino*-5-*thioformamido*-4-*methylpyrimidine* (I; $R_1 = H$, $R_2 = Me$), 6-*amino*-5-*thioformamido*-4-*ethylpyrimidine* (I; $R_1 = H$, $R_2 = Et$), and 2 : 6-*diamino*-5-*thioformamido*-4-*methylpyrimidine* (I; $R_1 = NH_2$, $R_2 = Me$) were prepared from the corresponding 5-amino-compounds; they are crystalline substances which evolve hydrogen sulphide above the melting point and yield the corresponding purines. On heating with chloroacetone, they yield the corresponding 3-pyrimidylthiazolium salts.

In the course of this work a considerable number of aminopyrimidines were prepared; most of these are known compounds, but 2-*amino*-6-*hydroxy*-4-*ethylpyrimidine* and 2 : 6-*diamino*-4-*ethylpyrimidine* have not hitherto been described. Neither could be thioformylated with potassium dithioformate.

Experimental.

5-*Thioacetamido*-4-*methyluracil* (II; R = Me).—5-Amino-4-methyluracil (1 g.) (Behrend, *Annalen*, 1885, **231**, 250), dissolved in dioxan (50 c.c.), was heated on the water-bath with di-

* Experiments by Miss A. Jacob.

thioacetic acid (0·9 g.) (Pohl, *Ber.*, 1907, **40**, 1304) during 4 hours. The mixture was cooled and diluted with light petroleum. The yellowish precipitate crystallised from hot water in colourless needles, m. p. 265—267° (Found: C, 42·4; H, 4·8; N, 21·1. $C_7H_9O_2N_3S$ requires C, 42·2; H, 4·6; N, 21·2%). Yield, quantitative.

5-*Thioformamido*-4-*methyluracil* (II; R = H).—5-Amino-4-methyluracil (1 g.) in dioxan (50 c.c.) was heated under reflux with dithioformic acid (0·7 g.) (Levi, *Atti R. Accad. Lincei*, 1923, **32**, I, 569). The crude *thioformyl* derivative precipitated with light petroleum was difficult to purify. After recrystallisation from water it had m. p. 260—262° (Found: N, 21·0. $C_6H_7O_2N_3S$ requires N, 22·7%. $C_6H_7O_2N_3S,H_2O$ requires N, 20·7%).

3-(2′: 6′-*Dihydroxy*-4′-*methylpyrimidyl*-5′)-4-*methylthiazolium Chloride*.—The above thioformyl compound (1 mol.), mixed with chloroacetone (4—5 mols.), was heated carefully over a free flame. Vigorous reaction occurred, and after 10—15 minutes the mixture was cooled, and the *product* precipitated as a gum by addition of ether. It crystallised from alcohol–acetone in colourless needles, m. p. 306° (decomp.) (Found: C, 40·9; H, 4·6; N, 15·6; Cl, 13·6. $C_9H_{11}O_2N_3ClS$ requires C, 41·4; H, 4·3; N, 16·1; Cl, 13·6%).

6-*Amino*-5-*thioformamido*-4-*methylpyrimidine* (I; R_1 = H, R_2 = Me).—To 5: 6-diamino-4-methylpyrimidine (1·5 g.) (Gabriel and Colman, *Ber.*, 1901, **34**, 1254), dissolved in water (10 c.c.), potassium dithioformate (2 g.) was added; traces of crystalline material, m. p. above 300°, soon separated. The solution was filtered and kept over sulphuric acid in a desiccator filled with carbon dioxide. After 12 hours the crystalline precipitate was collected (the filtrate may be treated with a further quantity of potassium dithioformate and the process repeated until the yield is nearly quantitative). The *thioformyl* compound crystallised from water in colourless needles (Found: C, 43·0; H, 5·2; S, 18·6. $C_6H_8N_4S$ requires C, 42·9; H, 4·8; S, 19·0%). It melted sharply at 168° with evolution of hydrogen sulphide; the melt resolidified and on further heating melted at 230°. Gabriel (*Ber.*, 1901, **34**, 1247) gives m. p. 235° for 4-methylpurine. Conversion into 4-methylpurine occurs slowly above 100°. The substance is very soluble in alcohol, less so in methyl alcohol, acetone and water, and insoluble in ether.

2-*Amino*-6-*hydroxy*-4-*ethylpyrimidine*.—A mixture of ethyl propionylacetate (13·3 g.) (Willstätter and Clarke, *Ber.*, 1914, **47**, 298), guanidine carbonate (8 g.), and absolute alcohol (25 c.c.) was heated under reflux for 4 hours, cooled, and the *product* filtered off and recrystallised from hot water; it formed colourless prisms (7 g.), m. p. 247—248° (Found: C, 51·6; H, 6·2; N, 29·6. $C_6H_9ON_3$ requires C, 51·8; H, 6·2; N, 30·2%). When it (1 g.) was heated with concentrated hydrochloric acid (6 c.c.) for 20 hours at 160°, 4-ethyluracil, m. p. 205°, was obtained (yield, 60%).

6-*Chloro*-2-*amino*-4-*ethylpyrimidine*.—A mixture of the above compound (3·5 g.) and phosphoryl chloride (10 c.c.) was heated under reflux for 2 hours. The resulting brownish solution was poured on ice and made alkaline with ammonia, and the precipitated *chloro*-compound collected. It crystallised from alcohol in colourless needles, m. p. 120—121° (yield, 60%) (Found: C, 45·2; H, 4·9; N, 26·1. $C_6H_8N_3Cl$ requires C, 45·7; H, 5·1; N, 26·7%).

2: 6-*Diamino*-4-*ethylpyrimidine*.—The above *chloro*-compound (0·6 g.) was heated with saturated alcoholic ammonia (20 c.c.) in a sealed tube at 180° during 6 hours. The alcohol was removed, the residue dissolved in a little water, and solid potassium hydroxide added. The precipitated *diamine* was collected and recrystallised from ethyl acetate containing a little light petroleum; it formed colourless needles, m. p. 160—161° (yield, 80%) (Found: N, 40·6. $C_6H_{10}N_4$ requires N, 40·6%).

6-*Amino*-5-*thioformamido*-4-*ethylpyrimidine* (I; R_1 = H, R_2 = Et).—5: 6-Diamino-4-ethylpyrimidine was prepared from 4-ethyluracil by a slight modification of Robinson and Tomlinson's method (J., 1935, 1283). The following process for isolating the diamine is simpler and gives much improved yields: The reaction mixture obtained on reduction of 2-chloro-5: 6-diamino-4-ethylpyrimidine is filtered, concentrated to remove alcohol, and diluted somewhat with water, and solid potassium hydroxide added. The precipitated diamine crystallises from ethyl acetate in large yellowish prisms, m. p. 164—165°; Robinson and Tomlinson (*loc. cit.*) give m. p. 159—161°. A further quantity may be obtained by extracting the alkaline mother-liquor with ethyl acetate (total yield, 60% or more).

The diamine (100 mg.), thioformylated in aqueous solution with potassium dithioformate in the manner described above, gave a *product* crystallising from water in colourless needles, m. p. 178° with evolution of hydrogen sulphide (yield, theoretical) (Found: C, 45·5; H, 6·0; S, 17·1. $C_7H_{10}N_4S$ requires C, 46·1; H, 5·5; S, 17·6%).

2: 6-*Diamino*-5-*thioformamido*-4-*methylpyrimidine* (I; R_1 = NH_2, R_2 = Me).—2: 5: 6-Triamino-4-methylpyrimidine (Gabriel and Colman, *loc. cit.*) on treatment with potassium

dithioformate as above gave colourless needles (from water), m. p. 255° with evolution of hydrogen sulphide (Found: S, 17·2. $C_6H_9N_5S$ requires S, 17·5%).

3-(2′ : 6′-*Diamino*-4′-*methylpyrimidyl*-5′)-4-*methylthiazolium Chloride Hydrochloride*.—To a solution of the above thioformyl compound (1 mol.) in acetone, chloroacetone (2 mols.) was added. The mixture was left for 3 days at room temperature, then diluted with an equal volume of alcohol, and refluxed for 4 hours. The colourless needles that separated were collected after cooling and recrystallised from alcohol–acetone containing hydrogen chloride; needles, m. p. 315° (decomp.), were obtained containing water of crystallisation, which was only expelled with difficulty (Found: C, 31·2; H, 5·4; N, 19·9; S, 9·0; Cl, 20·4. $C_9H_{13}N_5Cl_2S,3H_2O$ requires C, 31·0; H, 5·5; N, 20·1; S, 9·2; Cl, 20·4%). The corresponding picrate has m. p. 255°. On shaking with alkaline potassium ferricyanide, a substance is produced which, though non-fluorescent in visible light, is blue-fluorescent in ultra-violet light; the fluorescence disappears when the liquid is made acid, but reappears when it is made alkaline again.

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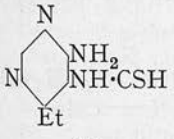
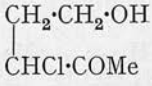
344. *Aneurin. Part V. The Synthesis of 3-Pyrimidylthiazolium Salts, including an Isomer of Aneurin.**

By A. R. Todd and F. Bergel.

Although 3-pyrimidylthiazolium salts can be synthesised by heating 5-thioformamidopyrimidines with chloroacetone (preceding paper), this simple method cannot be applied when chloroacetone is replaced by methyl α-chloro-γ-hydroxypropyl ketone, owing to the low reactivity of the latter substance. The difficulty can, however, be surmounted by using, in place of the free thioformamido-compound, its sodium salt. This condenses readily in absolute-alcoholic solution with α-halogenated ketones and the product, treated with hydrogen chloride, yields the desired 3-pyrimidylthiazolium salt. In this way, the sodium salt of 6-amino-5-thioformamido-4-ethylpyrimidine (I), condensed with methyl α-chloro-γ-hydroxypropyl ketone (II), yielded 3-(6′-*amino*-4′-*ethylpyrimidyl*-5′)-4-*methyl*-5-β-*hydroxyethylthiazolium chloride hydrochloride* (III; $R_1 = H$, $R_2 = Et$).



(I.)



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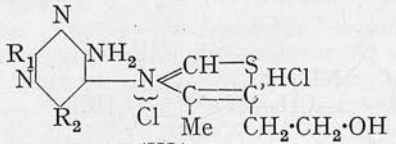


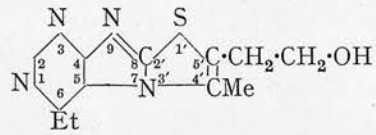
(III.)

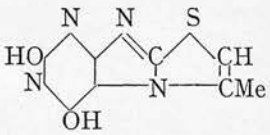
According to the original suggestion of Williams (*J. Amer. Chem. Soc.*, 1935, **57**, 229), (III; $R = H$, $R_2 = Et$) should have been identical with the hydrochloride of aneurin (vitamin B_1). This was not the case; in appearance and general solubilities the synthetic substance resembled the natural vitamin hydrochloride, but it melted much lower (220° as compared with 250°) and when tested on rats by the electrocardiographic method of Birch and Harris (*Biochem. J.*, 1934, **28**, 602) it showed no measurable physiological activity. Several other synthetic 3-pyrimidylthiazolium salts described in the experimental part of the paper were tested biologically with similar negative results, and none of them underwent fission with sodium sulphite in acid solution. The formaldehyde-azo-test of Kinnersley and Peters (*Biochem. J.*, 1934, **28**, 667) is given by (III; $R = H$, $R_2 = Et$) as well as by the actual vitamin. Our observations, however, suggest that a positive result in this test depends in some way on the presence of a β-hydroxyethyl group in position 5 and a hydrogen atom in position 2 of the thiazole nucleus. Thus 3-pyrimidylthiazolium salts without the β-hydroxyethyl group, the oxychlorovitamin of Buchman and Williams (*J. Amer.*

* A preliminary note on the results of this investigation has already been published by us (*Nature*, 1936, **138**, 76).

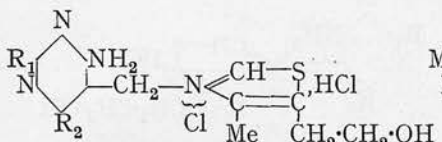
Chem. Soc., 1935, **68**, 1751), and thiochrome (Barger, Bergel, and Todd, *Ber.*, 1935, **68**, 2257) all give negative results.

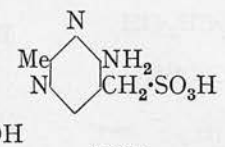
Any possibility that the vitamin might be represented by a closely related structure (III; $R_1 = R_2 = Me$) may be excluded on the following grounds. When synthetic 3-pyrimidylthiazolium salts containing an amino-group in position 6′ are oxidised with alkaline potassium ferricyanide under the conditions used for preparing thiochrome from aneurin, they yield solutions which, though blue-fluorescent in ultra-violet light, show no fluorescence whatever in visible light, in which thiochrome solutions fluoresce strongly. Evidence pointing in the same direction has been obtained in experiments carried out with a view to synthesising thiochrome, for which, on the basis of structure (III; $R = H$, $R_2 = Et$), we proposed the formula (IV) (Barger, Bergel, and Todd, *loc. cit.*).

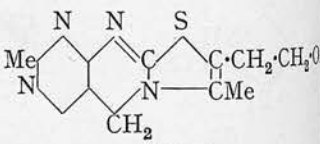
(IV.) 


(V.)

By analogy with 3-methylthiazolobenzimidazole (Todd, Bergel, and Karimullah, *Ber.*, 1936, **69**, 217) thiazolopurines of type (IV) should be capable of synthesis from 8-thiopurines and α-halogenated ketones. By this means Mr. B. A. Hems, B.Sc., prepared from 2 : 6-dihydroxy-8-thiopurine (Fischer, *Ber.*, 1898, **31**, 431) and chloroacetone the *substance* (V). This compound had a feeble though distinct fluorescence in ultra-violet light but none in visible light. In continuation we have condensed 8-thio-6-methylpurine (Gabriel, *Ber.*, 1901, **34**, 1254) and 8-*thio*-6-*ethylpurine* (prepared in a similar fashion from 4 : 5-diamino-6-ethylpyrimidine) with chloroacetone and with methyl α-chloro-γ-hydroxypropyl ketone (II); the products were not purified, but in neutral or alkaline solution they showed feeble blue fluorescence only when viewed in ultra-violet light. The non-fluorescence of thiazolopurines in visible light has recently been noted in addition by Ochiai (*Ber.*, 1936, **69**, 1650). The conclusion that thiochrome is not a thiazolopurine derivative is inevitable. On the available evidence it is clear that aneurin is not a 3-pyrimidylthiazolium salt. The only alternative structure which will accord with the properties of the vitamin is proposed by Makino and Imai (*Z. physiol. Chem.*, 1936, **239**, 1), namely (VI; $R = H$, $R_2 = Me$) or the closely related (VI; $R_1 = Me$, $R_2 = H$) differing only in the position of a methyl group.


(VI.)


(VII.)


(VIII.)

Simultaneously with the completion of this work, Williams (*J. Amer. Chem. Soc.*, 1936, **58**, 1063) announced that the pyrimidinesulphonic acid from the sulphite cleavage of aneurin has the structure (VII), and that aneurin itself is consequently (VI; $R_1 = Me$, $R_2 = H$). A synthesis of (VII) has also been recorded by Grewe (*Z. physiol. Chem.*, 1936, **242**, 89), who, however, does not describe the preparation of 6-amino-2-methyl-5-bromoethylpyrimidine, its immediate precursor; he also states that (VI; $R = Me$, $R_2 = H$) synthesised by the I.G. Farbenindustrie A.G. in their Elberfeld laboratories is identical with the vitamin.

On the basis of the vitamin formula (VI; $R = Me$, $R_2 = H$) thiochrome should have the structure (VIII); this is at present being investigated by synthetic methods.

Experimental.

3-(6′-*Amino*-4′-*ethylpyrimidyl*-5′)-4-*methyl*-5-β-*hydroxyethylthiazolium Chloride Hydrochloride* (III; $R_1 = H$, $R_2 = Et$).—To a mixture of 6-amino-5-thioformamido-4-ethylpyrimidine (108·5 mg.; 1 mol.) (preceding paper) and absolute alcohol (10 c.c.) was added a solution

sodium ethoxide in alcohol (1 c.c. containing 13·7 mg.; 1 atom Na). To the clear solution formed, methyl α-chloro-γ-hydroxypropyl ketone (0·1 c.c.; *i.e.*, excess) was added and the mixture left overnight at room temperature. After filtration from sodium chloride, alcoholic hydrogen chloride (0·3 c.c. containing 27·7 mg.; 1 mol. HCl) was added, and the solution heated under reflux for 4 hours. A further quantity of alcoholic hydrogen chloride (0·3 c.c.; 1 mol. HCl) was then added, heating continued for 1 hour, the solution cooled, and excess of acetone added to precipitate the quaternary *salt*, which crystallised in the ice-chest after a few hours. The hygroscopic product crystallised from alcohol–acetone in bundles of small colourless needles containing water of crystallisation. This was expelled at 100—110° and the salt then had m. p. 220° (decomp.) (Found: C, 41·1; H, 6·1; S, 8·5; Cl, 20·5. $C_{12}H_{18}ON_4Cl_2S,H_2O$ requires C, 40·6; H, 5·6; S, 9·0; Cl, 20·0%).

Oxidation with alkaline potassium ferricyanide gave solutions which, though non-fluorescent in visible light, had blue fluorescence in ultra-violet light. The formaldehyde–azo-test was positive and indistinguishable from that given by natural aneurin. Tested by the electrocardiagraphic method, 1·2 mg. contained less than 1 I.U. The inactivity of the substance was confirmed by Professor R. A. Peters, who kindly examined it, and to whom we wish to express our thanks.

3-(6′-*Amino*-4′-*ethylpyrimidyl*-5′)-4-*methylthiazolium Chloride Hydrochloride*.—6-Amino-5-thioformamido-4-ethylpyrimidine (108·5 g.) was converted into its sodium salt and condensed with chloroacetone (0·1 c.c.) in a manner similar to that described above, the total period of heating being in this case only 3 hours. The *product* crystallised from alcohol–acetone in hygroscopic colourless needles, m. p. 252—253° (decomp.) (Found: C, 40·6; H, 5·1; S, 10·5; Cl, 23·6. $C_{10}H_{14}N_4Cl_2S$ requires C, 40·9; H, 4·8; S, 10·9; Cl, 24·2%).

The substance reacted negative in the formaldehyde–azo-test and, tested by the electrocardiagraphic method, 2·8 mg. contained less than 1 I.U. Oxidation with alkaline potassium ferricyanide gave a solution which had weak blue fluorescence in ultra-violet light.

3-(6′-*Amino*-4′-*methylpyrimidyl*-5′)-4-*methyl*-5-β-*hydroxyethylthiazolium Chloride Hydrochloride* (III; $R_1 = H$, $R_2 = Me$).—6-Amino-5-thioformamido-4-methylpyrimidine (100 mg.) was converted into its sodium salt and condensed with methyl α-chloro-γ-hydroxypropyl ketone (0·1 c.c.) in the manner above described, the total period of heating being 5 hours. The *product* crystallised from alcohol–ethyl acetate in colourless needles, which lost water of crystallisation at 100—110° and melted and decomposed at 250° (Found: C, 38·8; H, 5·4; S, 8·5; Cl, 21·0. $C_{11}H_{16}ON_4Cl_2S,H_2O$ requires C, 38·7; H, 5·4; S, 9·4; Cl, 20·8%).

The substance gives a positive formaldehyde–azo-test and oxidation with alkaline potassium ferricyanide gives a solution which is blue fluorescent in ultra-violet light. Tested by the electrocardiagraphic method, 2·8 mg. contained less than 1 I.U.

3-(6′-*Amino*-4′-*methylpyrimidyl*-5′)-4-*methylthiazolium Chloride Hydrochloride*.—6-Amino-5-thioformamido-4-methylpyrimidine (100 mg.), condensed in the form of the sodium salt with chloroacetone (0·1 c.c.), the period of heating being 3 hours, gave a *product* crystallising from alcohol–acetone in needles, m. p. 254—255° (decomp.). Owing to its extremely hygroscopic character it was difficult to analyse (Found: C, 33·9; H, 5·7. $C_9H_{12}N_4Cl_2S,2H_2O$ requires C, 34·2; H, 5·1%). The substance did not give the formaldehyde–azo-test and, tested biologically by the electrocardiagraphic method, 5 mg. contained less than 1 I.U. Oxidation with alkaline potassium ferricyanide gave a solution blue-fluorescent in ultra-violet light.

2 : 6-*Dihydroxy*-8-*thiopurine*.—This substance was prepared by Fischer (*loc. cit.*) by heating bromoxanthine with potassium hydrogen sulphide. We obtained it in the following way: 4 : 5-diamino-2 : 6-dihydroxypyrimidine (1 mol.) (Traube, *Ber.*, 1900, **33**, 1382) was heated with thiourea (4 mols.) at 240—250° for 1 hour. The melt was cooled and extracted repeatedly with boiling water; the extract on cooling deposited a nearly colourless powder having the properties recorded by Fischer (*loc. cit.*) (Found in material dried at 150° in a high vacuum: N, 30·8. Calc. for $C_5H_4O_2N_4S$: N, 30·4%).

2 : 6-*Dihydroxy*-4′-*methylthiazolo*-(2′ : 3′ : 8 : 7)*purine* (V).—2 : 6-Dihydroxy-8-thiopurine (120 mg.) was boiled with chloroacetone (200 mg.) for 20 minutes, the mixture then being cooled and diluted with ether. The solid residue was recrystallised from a solution in hot dilute aqueous ammonia made weakly acid with acetic acid; on cooling, the *product* separated as a white micro-crystalline powder which did not melt below 250° (Found: C, 42·7; H, 2·8; N, 25·0; S, 14·7. $C_8H_6O_2N_4S$ requires C, 43·2; H, 2·7; N, 25·2; S, 14·4%). The substance is soluble in aqueous ammonia, caustic alkalis, and hydrochloric acid and insoluble in dilute acetic acid or cold water. A solution in concentrated aqueous ammonia gives no immediate precipitate with silver nitrate (distinction from 2 : 6-dihydroxy-8-thiopurine). Its ammoniacal solution

fluoresces light blue in ultra-violet light, the fluorescence disappearing when the solution is made acid.

8-*Thio*-6-*ethylpurine*.—4 : 5-Diamino-6-ethylpyrimidine (100 mg.) was heated with thiourea (150 mg.) at 170—180° for 1 hour; evolution of ammonia had then ceased. The melt was cooled, and triturated with water, and the insoluble residue dissolved in hot dilute aqueous ammonia. After treatment with charcoal and removal of the ammonia by boiling, the solution was cooled; it deposited yellowish needles, m. p. above 300° (Found: C, 46·9; H, 4·4. $C_7H_8N_4S$ requires C, 46·7; H, 4·4%).

Experiments on the Condensation of 4-*Methyl- and* 4-*Ethyl*-8-*thiopurines with* α-*Halogenated Ketones*.—The general method used was to heat the sodium derivative of the thiopurine with the appropriate halogenated ketone in alcoholic solution for 12 hours. The ketones used were chloroacetone and methyl α-chloro-γ-hydroxypropyl ketone; in every case solutions were obtained which when neutral or alkaline showed blue fluorescence in ultra-violet light, but no fluorescence in visible light could be detected. As the products were difficult to isolate in a pure state, the experiments were not pursued further, it being clear that no substances similar to thiochrome were obtainable in this way.

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